Defining Nonadherence and Nonpersistence to Anti-Vascular Endothelial Growth Factor Therapies in Neovascular Age-Related Macular Degeneration

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Defining non-adherence and non-persistence to anti-vascular endothelial growth factor therapies in age-related macular degeneration

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Key Points

Question

What is the definition of adherence to and persistence with intravitreal therapy in neovascular age-related macular degeneration?

Findings

This expert consensus survey used a modified Delphi technique to establish a set of definitions for the terms ‘adherence’, ‘non-adherence’, ‘persistence’, ‘non-persistence’ and ‘planned discontinuation or transfer of care’. A classification system based on the WHO dimensions of adherence was developed for the causes for non-adherence and non-persistence.

Meaning

These definitions provide a framework when assessing patient engagement to intravitreal therapy. This may be useful in future studies identifying rates or risk factors for patient non-adherence or non-persistence.

Word count: 97/100

Abstract

Importance

Poor adherence or persistence to treatment can be a barrier to optimizing clinical practice ('real-world') outcomes to intravitreal injection therapy in patients with neovascular age-related macular degeneration (nAMD). Currently there is a lack of consensus on the definition and classification of adherence, specific to this context.

Objective

To describe the development and validation of terminology related to patient non-adherence and non-persistence to anti-vascular endothelial growth factor (anti-VEGF) therapy.

Design, Setting and Participants

Following a systematic review of currently used terminology in the literature, a sub-committee panel of retinal experts developed a set of definitions and classification for validation. Definitions were restricted to use in patients with nAMD requiring intravitreal anti-VEGF therapy. Validation by the full nAMD Barometer Leadership Coalition was established using a modified Delphi approach, with pre-determined mean scores of ≥ 7.5 signifying consensus. Subsequent endorsement of the definitions was provided from a second set of retinal experts, with > 50% members agreeing or strongly agreeing with all definitions.

Main Outcomes and Measures

Development of consensus definitions for adherence and persistence and a classification system for the factors causing treatment non-adherence or non-persistence in patients with nAMD.

Results

'Non-adherence' was defined as missing two or more treatment or monitoring visits over a period of 12 months, with a visit considered missed if it exceeded > 2 weeks of the recommended date. 'Non-persistence' was defined by non-attendance or appointment not scheduled within the last six months. Additional terms of 'planned discontinuation and transfer of care' were also established. Causes of treatment non-adherence and non-persistence were classified into the following six dimensions: (1) patient-related, (2)

condition-related, (3) therapy-related, (4) health system-related (5) social/economic-related (6) other; with sub-categories specific to treatment for nAMD.

Conclusion & Relevance

This classification system provides a framework for assessing treatment non-adherence and non-persistence over time and across different health settings in the treatment of nAMD with current intravitreal anti-VEGF treatments. This may have additional importance given the potential association of the coronavirus pandemic on adherence to treatment in patients with nAMD.

Word count: 335/350

Introduction

Since its introduction, intravitreal anti-vascular endothelial growth factor (anti-VEGF) injection therapy has transformed the treatment of neovascular age-related macular degeneration (nAMD).[1] However, outcomes observed in clinical practice ('real-world') generally do not reach those seen in clinical trials,[2] potentially due to lack of adherence or non-persistence to the recommended trial regimens. Even within strict clinical trial settings, deviations from recommended protocols have often been associated with poorer visual outcomes, with a recent secondary analysis of the Comparison of Age-related Macular Degeneration Treatment Trial (CATT) reporting worse visual acuity at 2 years in patients with missed or delayed visits.[3]

The World Health Organization (WHO) defines adherence to long-term therapy as "the extent to which a person's behaviour, corresponds with agreed recommendations from a health care provider."[4] In contrast, persistence is defined as "the duration of time from initiation to discontinuation of therapy."[5] Previous discussions in ophthalmology have largely focused on how this behavior relates to outcomes in glaucoma therapy. The concept of what constitutes adherence and persistence in nAMD, however, has not been clearly established. A recent systematic review of factors affecting treatment non-adherence and non-persistence to anti-VEGF therapy in nAMD identified significant variations in both terminology and descriptions of adherence and persistence, concluding that uniform definitions, specific to this field, are required.[6]

The development of consensus definitions is important as it enables consistent reporting and comparison of the true prevalence of non-adherence and non-persistence. The effectiveness of proposed interventions can also be analyzed. In this study, we describe the development and validation of definitions for terms related to adherence and persistence to anti-VEGF therapies in nAMD.

Methods

<u>Sub-committee and validation group</u>

The nAMD Barometer Leadership Coalition is an international group of experts (n = 13 members) in the field of nAMD, vision care, and healthy aging. The nAMD Barometer program is a multi-phase initiative, established to develop robust evidence and provide recommendations on improving treatment in nAMD. As part of Phase 1 of this program, a subcommittee (n = 8 members) was formed to lead the development and consensus validation of terms relating to adherence and persistence in nAMD.

External endorsement of definitions was carried out by the wider members of the Vision Academy group. The Vision Academy is an international collaboration of more than 80 expert physicians who provide guidance on management of various retinal diseases (for full list of members, see https://www.visionacademy.org/vision-academy-community/the-faculty). Financial support for the nAMD Barometer program and the Vision Academy initiative is provided by Bayer Consumer Care AG, Switzerland.

Systematic literature review

A systematic review was conducted to identify original studies that included a definition of treatment adherence or persistence to anti-VEGF therapy for nAMD. Databases including MEDLINE, EMBASE, CENTRAL, were searched and results last updated on June 1 2019. No eligibility restrictions were placed on the type of anti-VEGF used or the treatment regimen employed. Studies were excluded if interventions other than anti-VEGF injections or retinal conditions other than nAMD were evaluated. Terms such as ‘compliance’, ‘non-attendance’, ‘discontinuation’, ‘drop-out’, ‘cessation’ and ‘lost-to-follow-up’ were considered synonymous. Current definitions and usage of non-adherence/non-persistence terms were extracted from the literature. The reasons for non-adherence and/or non-persistence were derived from publications included in a recently published systematic review conducted by the same nAMD Barometer group.[6]

Definition development, validation and endorsement

The term ‘adherence’, the preferred term in recent health literature, was chosen for validation as it reflects a more proactive healthcare interaction compared to the more passive term ‘compliance’.[4] The negative connotations of blame associated with the term ‘compliance’

have also led to its decreasing use. Similarly, the term ‘persistence’ was chosen instead of ‘discontinuation’ to mirror this shared health engaging behavior.

A modified Delphi approach was used to establish consensus definitions. Using the results of the systematic review as a starting point, proposed definitions for adherence and persistence were drafted. These initial definitions were discussed and refined amongst subcommittee members via virtual meetings and email correspondence to determine the most appropriate definitions to put forward for validation.

The Delphi method, a structured tool for establishing group consensus, was then used to validate the initial set of definitions.[7] This approach involves providing experts with a circulating series of questionnaires. After each round, the questionnaire is modified according to anonymized group feedback before it is resent, with the goal of working toward mutual agreement at the subsequent round. Specifically, for this study, a draft of the definitions and factors affecting treatment adherence/persistence developed by the subcommittee was circulated to the full Leadership Coalition for consensus validation. Each member of the Leadership Coalition was asked to assign a score from 1 to 10 to indicate their level of agreement with the proposed definitions, where 1 = strongly disagree and 10 = strongly agree. If respondents disagreed, they were required to provide anonymized feedback on reasons for disagreement and suggested changes to the proposed definition. The mean score from all respondents was calculated and a predetermined cut-off of ≥ 7.5 was established for consensus. If the mean score was ≥ 7.5, consensus was reached and the term validated. If the score was < 7.5, then consensus was not reached, and the definition was amended according to the feedback and sent back for a further round of evaluation. This process was repeated until consensus reached on all terms.

The validated set of definitions was then sent to the wider Vision Academy group members for endorsement via an online survey. Respondents were asked to rate their agreement with the proposed definitions as: strongly agree, agree, neither agree nor disagree, disagree, strongly disagree. A target of $> 50\%$ of members responding was required for the survey to be valid. Participants were also asked for their country of practice as well as the reimbursement status of treatment (ie, mostly reimbursed or mostly out-of-pocket) to

ascertain if this may have influenced the response. Biases were assessed using chi-square. Endorsement was established if ≥ 50% of respondents either agreed or strongly agreed.

Results

Current definitions in the literature

The systematic review identified 21 studies that reported definitions of compliance, adherence, persistence, discontinuation and/or loss to follow up. Additional insights into reasons for non-adherence and non-persistence were also included from nine studies. Definitions were extracted from the existing literature (Table 1).

Proposed definitions for adherence and persistence

A multi-stage modified Delphi approach was used to establish consensus on the proposed definitions (Figure 1). Further details are provided in Supplementary Materials: Appendix A.

The new validated definitions are described in Table 2. A single definition for each term was developed to ensure consistency and simplicity of use in everyday practice. To facilitate this, the validated definitions used attendance at any scheduled clinic visit (both monitoring and injection visits) as a measure of adherence or persistence. This enabled the terminology to be used across different injection regimens (eg, both pro-re-nata [PRN] and treat-and-extend [T&E]) as well as different practice settings.

Adherence/Non-adherence

The term ‘adherence’ was broken down into two categories: ‘fully adherent’ and ‘adherent’ (Table 2). The term ‘fully adherent’ refers to ideal practice, with complete observance of all scheduled visits. However, in clinical practice, this is often unrealistic, and most patients would be classified as non-adherent using this all-or-nothing approach. Therefore, a less stringent assessment of adherence was also established, to provide a step-down level of gauging adherence, which, although not perfect, was more achievable in clinical practice. A definition of no more than one missed appointment over a 12-month period was chosen, as

this reflects the commonly used definition of > 80% cut-off for classification of what constitutes 'good' adherence to general medications.[8,9] When a patient is non-adherent and misses appointments, the number of missed visits is determined by the total potential visits during the non-adherent period using the last known visit interval. For example, if a patient is recommended to have 4-weekly injections but does not return for 4 months, then the number of missed visits is 3, if the patient attends all follow up for the remaining 12-month period. If there is a further period of missed appointments within this 12-month period, the results are cumulative. Adherence is determined every 12 months so changes in adherence patterns over time can be assessed per year (eg, for a patient with three years of treatment, adherence is given per year, ie, for year 1, year 2, and year 3).

The timing of the visit was also considered important for calculating adherence, with a margin of two weeks delay allowed after which the physician-recommended visit is considered missed. The two-week cut off was based on logistics of scheduling appointments in clinical practice. Visits outside of this recommended timeframe are also recorded as missed, regardless of whether an appointment is actually booked. This will account for variations in healthcare models, with some systems requiring patients to call up and initiate the next appointment versus others where the clinic automatically makes the bookings. Delays due to systemic factors such as lack of clinic capacity as a cause for non-adherence will also be captured in this way.

For patients with bilateral nAMD, adherence is also calculated per patient rather than per eye, using the eye with the shortest visit interval for determination. For example, a patient on 12-weekly injections in one eye and 4-weekly in the fellow eye who does not attend any visits for 12 weeks is considered as non-adherent. This allows for factors such as bilaterality in disease or non-simultaneous injections to be easily identified as barriers to treatment.

Persistence/Non-persistence

The term 'non-persistence' was defined as non-attendance of any treatment or monitoring visit within the last 6 months. In determining the 6 months non-attendance cut-off, the subcommittee agreed that a 4-month period was too short as some T&E regimens allow extension up to 4 months (16 weeks). In contrast, 12 months was considered too long, as

there are very few circumstances in which patients would not have either a monitoring visit or injection for a full year and still be considered as engaging in therapy for nAMD.

Accordingly, a minimum assessment period of 6 months since first injection is required to gauge levels of persistence, as this is the least amount of time to elapse to meet the definition of non-persistence. For example, a patient who receives an injection and is scheduled to return in 4 weeks but does not return for either monitoring or further injections for 7 months would be considered non-persistent. However, if at the time of assessment, only 4 months had passed since their last visit, although the patient would be considered non-adherent (having missed 3 potential visits), persistence cannot be determined. The tolerance threshold of missed appointments for 'adherent' is still stricter than that allowed in the definition for 'persistence'. In this way, a patient could be classified as 'persistent' whilst not necessarily being 'adherent', but not vice-versa.

Planned Discontinuation or Transfer of Care

An additional term—'planned discontinuation or transfer of care'—was also developed to account for those patients for whom treatment cessation is intentional and not due to non-persistence. Patients are recorded as persistent if they attend visits with other physicians or clinics, as long as it is for the purpose of monitoring or treating their nAMD and it is possible to obtain ongoing treatment details. If a patient is known to have followed up with another physician but treatment details are not known, then the patient journey would be designated as 'transfer of care'.

<u>Proposed classification of factors affecting non-adherence and non-persistence</u>

The reasons for treatment non-adherence/non-persistence were classified according to the WHO dimensions of adherence[4]: (1) Patient-related, (2) condition-related, (3) therapy-related, (4) health systems/health care team factors (5) social/economic factors. Within these dimensions, subcategories specific to intravitreal therapy to nAMD were created (Table 3). The subcategories were determined based upon common factors identified from the

previously published systematic review.[6] There is no limit on number of factors per patient since reasons may be multifaceted or interrelated.

Discussion

There is currently no universal agreement of what adherence and persistence to intravitreal injection therapy is in nAMD. In this study, we provide a set of definitions that assess the extent and cause of treatment non-adherence or non-persistence, specific to this context.

The definitions proposed here are designed to be sufficiently flexible to cover all currently employed injection regimens for nAMD. Although there has been a transition to favoring T&E protocol in recent years, using timing of scheduled visits rather than number of injections enables these definitions to be used by practitioners across different health systems. However, it was decided to restrict these definitions and classification to therapy for nAMD with anti-VEGF only, as intravitreal injection is usually more time-critical in this condition, compared to other indications such as diabetic macular edema. The reasons behind non-adherence or non-persistence are also more likely to differ in this population of older patients, compared to those with macular edema from other retinal diseases.[10]

This new classification system also addresses some of the shortcomings in previous definitions, one of which was the grouping of ‘patient death’ or ‘planned discontinuation due to treatment futility’ with other causes of non-persistence.[6] Clearly, these represent different scenarios than patients who are non-persistent due to factors such as lack of transportation, for example. In addition, the distinction between the terminology ‘adherence’ and ‘persistence’ is also clarified here, as patients can be non-adherent yet still be persistent.

The classification system for causes of non-adherence or non-persistence was also modelled on the WHO dimensions of adherence but had subcategories specific to patients receiving intravitreal injections. This helps to align it with other discussions of adherence in the health literature yet keeps it relevant to management of nAMD. However, it is worth noting that although factors have been classified into distinct dimensions, causes can be bidirectional or interdependent. For example, a patient’s perceived treatment burden may be related to system

issues such as distance to specialist treatment, which is also related to social barriers such as access to transport. Therefore, for an individual patient, there can be multiple attributable reasons.

There are several potential limitations to the proposed classification system. Firstly, these definitions were established from consensus opinions and have yet to be tested on patient datasets. This is similar to the development of other classification systems currently in use, such as the Classification of Atrophy Meeting for definitions of atrophy associated with AMD, which was established using expert consensus. However, the clinical relevance of our proposed system will be examined in the next phase of the nAMD Barometer initiative, in which these definitions will be used in observational studies of patients, clinicians, and caregivers and their perceptions of barriers to treatment.

A further limitation to this classification system is that these were established in the setting of an industry-sponsored group, which could introduce subconscious bias to the recommendations. The use of objective evidence, such as the systematic literature review and the WHO dimensions of adherence as the starting basis for developing the definitions is intended to minimize any potential bias.

An additional consideration is that the maximum number of missed visits allowed to still be considered as adherent was one per 12-month period, which may not truly reflect all currently used treatment regimens. The rationale for only 1 visit was based on a treat-and-extend regimen in the first year. The absolute minimum number of injections in the first 12 months, assuming a loading dose of 3 injections followed by a 2-weekly extension at every visit, would be approximately 6 injections, and the 80% calculation refers to this scenario. However, although T&E is increasingly preferred, not every physician or health system employs this regimen. Furthermore, the minimum number of injections per 12-month period will depend on the patient's disease activity and where they are in their treatment trajectory. For example, a patient may be on a 16-weekly interval in their third year of treatment for which an adherence rate of 80% would be 2.4 visits out of 3 expected per year. Nevertheless, to provide ease of use and better reflect the critical aspect of the first year of treatment, we felt that using a constant and whole number (ie, missing no more than 1 visit per 12 months) rather than percentage of visits was a reasonable compromise. Finally, usage of this proposed classification system may be limited when used in studies where the intended treatment

schedule is not recorded. For example, in some electronic or insurance databases, only the actual date of visit may be recorded. Therefore, missed visits or visits outside the 2-week margin may not necessarily be detected.

Understanding the prevalence and reasons behind non-adherence and non-persistence is important, as it remains a significant barrier to optimizing outcomes for patients with nAMD. The validated definitions and classification system proposed in this paper provide an opportunity to raise awareness among healthcare professionals and patients. It also sets out a uniform language for use in future research for easier comparison. The current COVID-19 pandemic in particular, has presented unprecedented challenges for patient management. It is likely that a significant proportion of nAMD patients will have had their treatment interrupted during this crisis.[11] Consistent terminology will be important as we begin to assess the impact of the pandemic on patient outcomes.

Consensus definitions also establish benchmarks to measure the effectiveness of interventions designed to improve adherence and persistence to anti-VEGF injections. As part of the nAMD Barometer project, initiatives currently underway include quantifying non-adherence and non-persistence using this proposed framework in two separate studies. The first is a qualitative observational study using interviews with patients and caregivers (both adherent and non-adherent) to determine barriers and assess its impact on visual outcomes. The second is an audience-specific survey of physicians, clinic staff, and patients intended to quantify perspectives, cultural and healthcare system differences, and to correlate these risk factors with their effect on adherence. Future studies could examine whether a tool for triaging and identifying at-risk individuals can help modify outcomes. Ultimately, the goal will be to develop meaningful interventions, tailored according to the patient, physician and health system.

Word count: 3992/3000

List of Figures

Figure 1. Modified Delphi consensus process and development of validated definitions.

Figure legend. *n*AMD: neovascular age-related macular degeneration; WHO: World Health Organisation

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Supplementary Materials

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476 Table 1. Current definitions extracted from the systematic review
477

Term	Definitions in the existing literature
Non-adherence Synonyms: Non-compliance Absenteeism Non-attendance	• No treatment or monitoring visit at least once every 6 weeks or 8 weeks • Extreme violation of prescribed treatment regimen • Non-attendance at every clinic appointment • Less than 8 injections over 12 months • Visits outside of the prescribed 28 days ± 7-day window
Non-persistence Synonyms: Discontinuation Drop-out Cessation Lost-to follow up	• Treatment discontinuation before initial 12 months, study period, or permanently • No treatment or monitoring visit for 4, 6, 12, or 24 months • No follow up by an ophthalmologist for 3 months • No follow up within a 12-month period after receiving at least one anti-VEGF injection

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480 Table 2. Validated definitions for adherence and persistence to intravitreal therapy in neovascular age-related macular degeneration (nAMD)
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Term	Definition	Mean Stage 1 Delphi Score	Mean Stage 2 Delphi Score
Adherence	A patient is considered ***fully adherent*** to anti-VEGF therapy in nAMD if: • They attend every scheduled clinic visit (treatment or monitoring), and undergo every treatment or monitoring procedure advised by the treating physician over a period of 12 months	9.69	9.91
	A patient is considered ***adherent*** to anti-VEGF therapy in nAMD if: • They miss no more than one treatment or monitoring visit scheduled as advised by the treating physician over a period of 12 months Note: • A visit is considered missed if the recommended appointment date is exceeded by >2 weeks for any reason • The number of missed visits is determined based on the total potential visits missed during the non-adherent period using the last recommended visit interval • The period of 12 months begins from the time of the first injection. For subsequent years of treatment, adherence is calculated every 12 months	8.75	9.82
Non-adherence	A patient is considered non-adherent to anti-VEGF therapy in nAMD if: • They miss two or more treatment or monitoring visits scheduled as advised by the treating physician over a period of 12 months Note: • A visit is considered missed if the recommended appointment date is exceeded by >2 weeks for any reason • The number of missed visits is determined based on the total potential visits missed during the non-adherent period using the last recommended visit interval	8.33	9.67
Persistence	A patient is considered persistent to anti-VEGF therapy in nAMD if: • They maintain treatment or monitoring as advised by the treating physician AND attended their most recent appointment within the last six months Note: • A patient is not required to be adherent in order to be persistent	9.31	9.82

	• A minimum of 6 months observation since first injection is required to assess persistence		
Non-persistence	A patient is considered non-persistent to anti-VEGF therapy in nAMD if: • They do not attend any treatment or monitoring visit for any reason within the last six months OR • Follow-up appointments are not scheduled for any reason for a period of six months Note: • The first day of the 6-month period after the most recent appointment attended should serve as the onset of non-persistence date A minimum of 6 months since first injection is required to assess persistence	9.50	9.27
Planned discontinuation or transfer of care	A patient is considered to have a planned discontinuation as defined by: • Lack of treatment response (treatment futility) judged by the treating physician • No disease activity requiring ongoing treatment judged by the treating physician A patient is considered to have their care transferred if: • The ongoing management of the patient's nAMD is transferred to another physician	N/A	9.27

Anti-VEGF: anti-vascular endothelial growth factor therapy; nAMD: neovascular age-related macular degeneration

Table 3. Validated classification of causes of treatment non-adherence or non-persistence to therapy in neovascular age-related macular degeneration (nAMD)

Classification	Sub-categories	Mean Delphi Score
Patient-related	• Patient education level/understanding of need for treatment • Patient loss of motivation • Ocular comorbidities • Non-ocular comorbidities/general health • Consent withdrawal • Treatment burden • Other	9.27
Condition-related	• Treatment success (patient-determined) • Treatment failure (patient-determined) • Treatment contraindication • Poor baseline vision • Other	9.27
Therapy-related	• Treatment discomfort • Adverse event • Fear of injections • Other	8.64
Health system/ Healthcare team	• Administrative problem • Access to treatment (eg, appointment availability) • Distance to treatment • Other	8.73
Social/economic-related	• Lack of transport • Caregiver availability (eg, to attend clinic appointment with patient) • Direct cost/reimbursement issue • Indirect costs (e.g. parking fees, productivity loss) • Other	8.82
Other	• Death • Uncontrollable/unpredictable event (eg, restrictions or deferral of appointment due to COVID-19 pandemic)	9.64