Can the Onset of Neovascular Age-Related Macular Degeneration Be an Acceptable Endpoint for Prophylactic Clinical Trials?

Luísa S.M. Mendonçaab, Emily S. Levenec, Nadia K. Waheed

aNew England Eye Center, Tufts Medical Center, Boston, MA, USA; bDepartment of Ophthalmology, Federal University of São Paulo, São Paulo, Brazil; cTufts University School of Medicine, Boston, MA, USA

Keywords
Prophylactic clinical trials · Clinical trial endpoints · Age-related macular degeneration (AMD) · Intermediate AMD · Neovascular AMD

Abstract
Many studies over the past 20 years have pursued the goal of preventing or deferring progression from early and intermediate age-related macular degeneration (AMD) to advanced AMD. The onset of neovascular AMD has been used as a primary endpoint in some prophylactic clinical trials because it is easy to assess and relatively well-defined. Nevertheless, the use of this endpoint for assessing progression of AMD lacks validation. The aims of this paper are to review the current practice of clinical trials investigating the prevention of progression of early or intermediate AMD to neovascular AMD, so-called prophylactic trials, as well as identify ongoing efforts to standardize endpoints and select the ideal population for such studies.

Introduction
Age-related macular degeneration (AMD) is one of the leading causes of blindness worldwide [1–3]. There are several reasons for this. There is no therapy available that prevents the development of geographic atrophy (GA), an end-stage manifestation of AMD. Also, while antiangiogenic drugs have dramatically altered the prognosis of neovascular AMD, studies have shown that, in the long term, patients lose vision because of scarring and macular atrophy [4]. The SEVEN-UP study found a mean loss of 8.6 letters over a mean of 7.3 years (vs. baseline) at entry into the ANCHOR or MARINA trials, and a loss of 19.8 letters over approximately 5 years compared to the visual acuity at the completion of the trials [4].

Clearly, there is still much to be done to achieve better visual results in patients with AMD. Identification of new therapeutic targets may be one path. While testing treatments for the advanced stages of disease, i.e., long-lasting intravitreal drugs, complement inhibitors, and gene therapy, is one approach, it may well be that, once patients are far enough advanced along the AMD pathway, the benefits to be obtained from therapy are limited. Indeed, the...
key for achieving better visual results might lie in the prevention of progression from early and intermediate stages to late AMD. However, this presents a challenging dilemma. Prophylactic trials, which are studies that aim to prevent the development of advanced AMD in eyes at early and intermediate stages, would need to be very long (several years) and very large to achieve adequate statistical power. On the other hand, the endpoints available that can act as surrogate markers for progression and could shorten the duration of such clinical trials, either show a large amount of variability or are imperfect in predicting progression. Overall, both strategies are likely to involve high costs.

This paper focuses on the onset of neovascular AMD as a clinical trial endpoint for prophylactic studies. We discuss how past studies in the field were conducted and identify ongoing efforts to standardize endpoints for such studies. We also look, to a more limited extent, at identifying characteristics that can be used to enrich high-risk populations enrolled in such clinical trials and thereby help reduce the cost of these trials. Finally, we briefly discuss endpoints that can potentially be used as surrogates for neovascular AMD onset, when time to outcome is critical.

**Prophylactic Clinical Trial Endpoints: Where Do We Stand?**

For clinical trials of ophthalmic diseases, visual acuity is almost always used as a gold standard endpoint. However, changes in visual acuity are more prominent in the later stages of disease than in the early stages [1, 5, 6]. This makes visual acuity assessment impractical as a measure of progression in intermediate AMD because it may require several years of observation to demonstrate changes [1, 5]. Thus, an effective surrogate endpoint is needed; this would be one that correlates well with visual acuity but shows changes over a shorter period of time and could therefore be used to reduce the duration of clinical trials. Surrogate endpoints need to be objective, easy to interpret, reproducible, sensitive, and specific, and to correlate well with disease progression and, ultimately, visual acuity. In the context of prophylactic trials of AMD, neovascular onset has been used as a surrogate endpoint by several studies.

The Age-Related Eye Disease Study (AREDS) is a classic and well-known example of a clinical trial designed to assess AMD progression as a primary endpoint. It tested oral antioxidants and zinc as a novel intervention, with the endpoint being progression to advanced AMD, defined either as macular neovascularization (MNV) or center-involving GA [7]. In the pre-optical coherence tomography (OCT) era, macular neovascularization (MNV) onset was diagnosed in this study using color fundus photographs (CFP) [8, 9].

Recently, the Intravitreal Aflibercept Injection versus Sham as Prophylaxis against Conversion to Neovascular AMD (PRO-CON) Study (NCT02462889), a clinical trial designed to test the efficacy of aflibercept to prevent high-risk intermediate AMD patients from progressing to exudative AMD, used the proportion of patients converting to neovascular AMD over a 24-month follow-up as its primary outcome using OCT and fluorescein angiography (FA) [10, 11]. High-risk intermediate AMD was defined in this study as the presence of >10 intermediate drusen or 1 large drusen in the study eye and neovascular AMD in the fellow eye [10]. The study failed to prove the efficacy of the therapy (unpublished data); however, as a pioneer study testing invasive therapies for intermediate AMD, it highlighted the importance of proper patient selection including consideration of the risk-benefit ratio for inclusion in interventional prophylactic trials when there is no standard of care for their disease stage.

The Laser Intervention in Early Age-Related Macular Degeneration (LEAD) randomized clinical trial recently tested subthreshold nanosecond laser intervention in eyes with intermediate AMD and bilateral large drusen to prevent progression to advanced stages, either MNV or GA. The trial failed to demonstrate benefits in reducing progression in the overall population. However, it did show an effect modification, in which progression was slowed in eyes without reticular pseudodrusen but increased in eyes presenting with reticular pseudodrusen [12].

The Open-Label Phase 1 Clinical Study to Evaluate the Safety and Tolerability of Subcutaneous Elamipretide in Subjects with Intermediate AMD (ReCLAIM) study (NCT02848313) also enrolled high-risk intermediate AMD patients, defined as having either at least 1 large drusen or multiple medium-sized drusen, in order to test the safety and tolerability of subcutaneous elamipretide which is designed to treat mitochondrial dysfunction secondary to oxidative stress [13]. Because it was a phase I study, efficacy was not assessed, and therefore onset of progression was not an endpoint. A phase II study is now enrolling patients with non-central GA with low-luminance best-corrected visual acuity (LLVA) as its primary endpoint [14].
Despite many prophylactic clinical trials defining progression to advanced AMD with a composite primary endpoint (combining the onset of neovascular AMD and GA), such as the AREDS and the LEAD trial noted above, it is important to emphasize that these 2 forms of macular degeneration have separate pathophysiological pathways. Although using a composite endpoint often results in a smaller required sample size and lower study costs, the research question may remain unanswered when a therapy works better for preventing progression to only 1 of the advanced AMD types. Ideally, 3 recommendations need to be met before using a composite endpoint: both components should be similar in importance to the patient, have similar incidences, and be similarly affected by the intervention [15]. Although GA and MNV are equally important complications for the patient, the frequencies and risk factors for the occurrence of these 2 forms of disease are different, as are the treatment options. Henceforth, we discuss here the use of neovascular onset as a primary endpoint but will also cite features associated with GA progression as some are common to both advanced forms of AMD.

There are still no validated surrogate outcome measures or endpoints accepted by regulatory agencies specifically for drug development for intermediate AMD [5]. The currently accepted surrogate endpoints refer to eyes with late stages of disease: GA growth rate for late dry AMD, and fluid on OCT and leakage on FA for neovascular AMD. However, there are ongoing studies aiming to validate endpoints for prophylactic trials in intermediate AMD populations. The MACUSTAR consortium is a multicenter initiative to establish functional, morphological, and self-reported outcomes in intermediate AMD [5]. Morphological assessments used to identify the onset of MNV and GA included spectral domain OCT, CFP, and FA. The IMPACT study (NCT03688243) is a multicenter clinical trial currently enrolling intermediate AMD patients to investigate and establish robust and repeatable anatomic and vascular metrics. The study uses OCT and OCT angiography (OCTA) markers such as choriocapillaris (CC) nonperfusion, drusen volume, detection of nonexudative MNV at baseline, and other structural OCT markers [16].

Progression to neovascular AMD is a promising endpoint for medications that potentially inhibit angiogenic signals. There are several advantages to this endpoint. One, it is relatively unambiguous and easy to assess using traditional imaging modalities that are present in most clinical settings. Second, it has been associated with progression of disease, and ultimately with loss of visual acuity [9, 17]. Thus, it meets most of the criteria required for a surrogate endpoint. It is worth noting that the development of nonexudative MNV can be protective in eyes with atrophy, preventing its enlargement within the area of MNV [18, 19]. Therefore, when choosing surrogate endpoints for loss of function, MNV onset followed by exudation would be the outcome to be used, rather than MNV development in general.

In the context of exudative MNV as a primary endpoint, important design aspects should be considered. Studies need to be carefully powered so as to have a large enough sample size to demonstrate differences in conversion rates with treatment. The AREDS reported a 10% conversion rate in patients that presented with nonadvanced AMD in both eyes. When considering the fellow eyes of patients with unilateral neovascular AMD, the rate of conversion was around 35% in a relatively long follow-up of 6.3 years [20]. In a post hoc analysis of the MARINA and ANCHOR studies, the rates of conversion of fellow eyes were 15.9–26.4% at 12 months and 23.8–38.8% at 24 months [21]. An analysis of the fellow eyes of patients enrolled in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) revealed an incidence of neovascular AMD of 20.3% at 24 months [22]. A post hoc analysis of fellow eyes in the HARBOR trial found a 12.2% progression rate to exudative MNV at 2 years, based exclusively on SD-OCT analysis of eligible patients [23]. The PRO-CON study, which had as an inclusion criterion the presence of neovascular AMD in the fellow eye, identified progression to neovascular AMD in 9.38 and 10.90% of eyes in the sham group at months 12 and 24, respectively [10]. These differences in rates of progression among intermediate AMD patients, as well as the varying times to conversion, highlight the importance of proper choice of inclusion criteria and targeting subjects that are more likely to progress over a given interval.

In most prophylactic clinical trials (e.g., PRO-CON and LEAD), inclusion criteria consider the risk of an eye converting to exudative MNV. This is important to adequately power the study, but is also relevant when invasive therapies are tested. Since many patients will not actually benefit from treatment, considering the risk-benefit ratio for inclusion in a prophylactic trial is important. Several strategies can be employed to enrich the study with subjects who are more likely to convert, which has the dual benefit of allowing for a lower sample size or shorter follow-up duration as well as increasing the benefit-risk ratio to the patients. These strategies are discussed below.
Optimizing Prophylactic Clinical Trials: Inclusion Criteria Based on Risk Factors

Several scales that include demographic, environmental, and genetic factors as well as imaging biomarkers to predict progression in intermediate AMD have been published to allow for the selection of high-risk patients for enrollment in such clinical trials [2, 23–27]. Models that assess time-to-progression are particularly useful as references for designing clinical trials that, in general, last 2 years.

Age, family history, smoking status, advanced AMD in the fellow eye, genetic variants (CFH Y402H and ARMS2 A69S), and imaging features like large drusen (Fig. 1) and pigmentary changes on CFP, were found to correlate with progression to advanced AMD, both GA or MNV, in a multivariate analysis [2]. Considering the status of the fellow eye at baseline, patients with MNV in the fellow eye were more likely to progress to MNV, while patients with GA in the fellow eye were more likely to progress to GA [2]. Additionally, conversion to MNV in the fellow eye in the past 2 years was associated with a higher risk of conversion of MNV in the study eye compared to a conversion that happened >2 years prior (unpublished data).

An association between OCT features in intermediate AMD and progression to MNV has also been extensively investigated. Hyperreflective foci (HRF) (Fig. 2), hyporeflective foci within drusenoid lesions, subretinal drusenoid deposits (also called reticular pseudodrusen), (Fig. 1) and RPE thickening have been associated with progression to MNV [3, 23, 28–30].

A recently published state-of-the-art machine-learning study developed predictive models for MNV and GA development in a cohort of intermediate AMD eyes based on OCT features that were identified by means of artificial intelligence (AI) tools combined with demographic

Fig. 1. Intermediate age-related macular degeneration (AMD) (a–c) with progression to exudative macular neovascularization (MNV) (d–f). a Color fundus photo shows numerous large drusen (white arrows) in the macula at baseline. Optical coherence tomography (OCT) en face (b) and B-scan (c) show a subretinal drusenoid deposit (white square), sub-retinal pigment epithelium (RPE) drusen, and drusenoid pigment epithelium detachment (white asterisk) at baseline. d Fluorescein angiography with dye leakage, stippled fluorescence (yellow asterisk) and late staining (red arrow) consistent with a type 1 MNV that developed 24 months after baseline images. OCT en face (e) and B-scan (f) show subretinal drusenoid deposits (white square) above a RPE detachment due to a type 1 MNV with subretinal fluid (yellow arrow).
and genetic data. The authors found that drusen-centric metrics (e.g., RPE + drusen volume and thickness, but not drusen volume or area alone) seemed more relevant to the progression to MNV whereas neurosensory retinal changes and age were more relevant to the development of GA [3]. For both outcomes, hyperreflective foci were highly weighted in the model and represented the second most important feature; this confirmed findings of earlier studies that showed that pigmentary changes correlate with progression to both advanced forms of AMD [2, 3, 31]. Therefore, the presence of hyperreflective foci should be considered a relevant risk factor for AMD progression in general.

Other AI models have been proposed, using either OCT or CFP to predict progression to exudative MNV, with satisfactory accuracy [32, 33]. Markers used for prediction in these studies are mainly drusen and pigmentary changes on CFP [32], and segmentation of external layers on OCT. Pixels under the RPE were used to identify progressors, as opposed to pixels around the RPE that had a higher impact on identifying nonprogressors as per occlusion sensitivity analysis [33]. More recently, Yim et al. [34] developed a model to predict progression to neovascular AMD within 6 months, using deep learning for performing both a comprehensive feature extraction on OCT and prediction. Interestingly, the authors proposed
configurable operating points, allowing different balances between sensitivity and specificity.

It has been shown that increases in drusen volume and area in 2 years predicts progression to neovascular AMD [29, 30], so the variability of those measures should also be taken into account when selecting patients at risk for progression [3, 29]. There have been conflicting results in the literature regarding the interval at which drusen volume is capable of predicting progression. The study of de Sisternes et al. [24] showed that drusen volume and area were predictors of MNV development after 24 months; other groups demonstrated the significance of these metrics for predicting progression within 2 years [3, 23, 28, 29]. This discrepancy might be due to differences regarding other risk factors in these populations.

The value of functional metrics, such as microperimetry and low-luminance visual acuity, for predicting progression to advanced AMD has recently been studied. These metrics failed to improve the predictive performance of a model that included pigmentary abnormalities and drusen, as graded on CFP [35].

It is known that eyes with nonexudative or subclinical MNV (Fig. 3) present a higher risk of progression to exudation than do eyes with drusen-only intermediate AMD [36, 37]. A longitudinal study employing swept-source (SS)-OCTA for detecting nonexudative MNV demonstrated a 15.2-fold increase in the risk of exudation in eyes with this finding versus eyes without nonexudative MNV [36]. Therefore, it is important at the baseline to identify nonexudative MNV in patients with intermediate AMD enrolled in prophylactic clinical trials, defining a separate subgroup analysis for this condition, or balancing it between the control and treatment group to ensure a proper interpretation of results. The IMPACT study has, amongst its aims, the purpose of investigating the presence of nonexudative AMD at baseline in eyes otherwise classified as intermediate AMD using SS-OCTA [16]. A standardization of this assessment may be useful for future clinical trials that may adopt OCTA testing at baseline for all eyes with intermediate AMD.

Studies that specifically evaluate the prevention of nonexudative MNV conversion are also needed. The PRO-CON study did not demonstrate reduced progression rates in eyes that had nonexudative MNV, but this trial was not designed or powered for this purpose [10]. It is important to establish in advance how to interpret the development of nonexudative MNV throughout follow-up, e.g., if this finding is identified as a positive conversion or if the presence of exudation is necessary to mark a conversion, the latter being the better option when using a surrogate endpoint for function as the intended strategy.

**Other Potential Surrogate Endpoints in Prophylactic Clinical Trials**

When the duration of the study is a concern, and a shorter follow-up is desired by the sponsor, an alternative approach to using the onset of neovascular AMD may be
Prophylactic clinical trials are imperative for changing long-term achievable visual results in AMD. Despite recent efforts, therapies to prevent or defer progression from early and intermediate AMD to advanced stages have not succeeded. Currently, many prophylactic studies use the onset of neovascular AMD as the primary endpoint, or a composite primary endpoint that combines progression to GA and neovascular AMD. Based on current knowledge, it is reasonable to state that neovascular onset is an acceptable endpoint for prophylactic trials, as it is easy to assess and relatively well-defined. It can also be enriched using strategies such as identifying eyes with a higher risk for progression, as there is robust literature available on risk factors for progression to neovascular AMD.

**Conclusion**

Prophylactic clinical trials are imperative for changing long-term achievable visual results in AMD. Despite recent efforts, therapies to prevent or defer progression from early and intermediate AMD to advanced stages have not succeeded. Currently, many prophylactic studies use the onset of neovascular AMD as the primary endpoint, or a composite primary endpoint that combines progression to GA and neovascular AMD. Based on current knowledge, it is reasonable to state that neovascular onset is an acceptable endpoint for prophylactic trials, as it is easy to assess and relatively well-defined. It can also be enriched using strategies such as identifying eyes with a higher risk for progression, as there is robust literature available on risk factors for progression to neovascular AMD.

**Conflict of Interest Statement**

L.S.M.M. and E.S.L. have no conflicts of interest to declare.

**Funding Sources**

The authors report grants from Massachusetts Lions Club and Research to Prevent Blindness. L.S.M.M. reports a research scholarship granted by CAPES, Ministry of Education, Brazil (in the scope of Capes-PrInt program, process No. 88887.369769/2019–00).

**Author Contributions**

L.S.M.M. performed the literature review and worked on manuscript conceptualization and drafting. E.S.L. worked on the drafting and critical review of the manuscript. N.K.W. performed the literature review and worked on conceptualization, drafting, and critical review of the manuscript.

**References**


