DOI: https://doi.org/10.4038/jcosl.v30i1.88

*College lecture – 2023*

# Late stage AMD: can we do better?

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*The Journal of the College of Ophthalmologists of Sri Lanka 2024; 30: 14-19*


## Abstract

*Both late, vision threatening forms of age-related macular degeneration (AMD) still present major unmet needs. In neovascular AMD (nAMD) there is still significant research activity underway in trying to improve our interventions. However, it is likely that by looking at how current treatments are being used, we will gain a better understanding of how to improve outcomes for all patients. Clinicians use different treatment protocols and have different optical coherence tomography defined goals of treatment, which potentially impacts outcomes. Real-world outcome study in nAMD, such as the Voyager study aim to identify treatment patterns and determine the best strategies to improve outcomes globally.*

*In geographic atrophy (GA), there is an extraordinary effort underway to find treatments for this late form of AMD, which until now has had no interventions available to slow its progression or prevent its occurrence. In 2023 the first two treatments for GA received approval in the United States. As treatments become available, for patients with established areas of cell loss, the focus will turn to the possibility to using these interventions earlier in the disease process. Earlier intervention trials however, require different trial design to ensure greater feasibility in terms of cost and length. Earlier surrogate trial endpoints for GA have been proposed, such as nascent GA (nGA), which could help trial design, but additional natural history studies in AMD need to be undertaken, such as the HONU study. In addition, when considering the possibility of novel early intervention, different AMD sub-phenotypes may well need to be considered as they may respond differently to the intervention being investigated, such as was the case in the LEAD nanosecond laser study.*


**COI:** Apellis, Roche/Genentech, Bayer, Novartis, Belite Bio, Boehringer Ingelheim Pharmaceuticals, Character Bioscience, Janssen, AbbVie Astellas

## Introduction

There are several different nomenclature schemes and grading stages used when considering age-related macular degeneration (AMD) and this can lead to some confusion when talking about AMD. The Beckman classification system[1] defines AMD as either early, intermediate or late-stage disease. Late-stage disease is divided into either neovascular AMD (nAMD) or geographic atrophy (GA). In Beckman "dry" AMD is only used when referring to late-stage geographic atrophy (GA) and not for earlier stages of non neovascular AMD. In this way when someone refers to dry AMD there is no ambiguity as to what stage of non neovascular disease is being referred to – it is only GA. To date most activity in terms of intervention trials in AMD have been concerned with these two late stages of AMD, whilst new treatments for the earlier, non late AMD stages of this disease remains to be discovered.

## Neovascular AMD

The past two decade has seen great advances in the treatment of nAMD, or wet AMD. Anti vascular endothelial growth factor (VEGF) treatments have revolutionized the outcome for people with this devastating late form of AMD. However, what has become clear is that, overall, the real-world outcomes are not as good as those achieved in the pivotal clinical trials[2-8].

In the first 1-2 years of treatment, undertreatment for a variety of reasons has been considered a major cause of this disparity in outcome and to address this need, many pharmaceutical companies are working to bring longer acting drugs to market. Longer duration treatments should help to reduce the impact of undertreatment, with longer acting interventions reducing the multiple burdens associated with the need for frequent attendance to a health professional to receive treatment. However, even with best practise

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and apparent adequate treatment, vision is often still lost in the mid-term over several years. For example, in a study undertaken in the United Kingdom, looking at the 10 year outcomes with anti VEGF treatment, vision appeared to remain stable for the first 4 years but thereafter declined over time[9].

Indeed, Finger et al, utilized the Fight Retinal Blindness registry to model outcomes using real-world cohort data on patients with nAMD treated in routine eye clinics in Australia, New Zealand and Switzerland between 2007 and 2015. Using over 67 000 visits, they reported that for the mean remaining lifetime of 11 years, it was estimated that only 12% of the sample would retained driving visual acuity and an estimated 15% would retained reading vision in at least one eye[10].

One current area of focus in nAMD is the realisation that the loss of vision is not necessarily the result of a poor response to anti-VEGF but rather the onset of atrophy and fibrosis in eyes with nAMD. In many instances the anti-VEGF response has been complete and intervals increased, yet vision is reducing due to subfoveal atrophy and/or fibrosis, where neither pathology is addressed with an anti-VEGF agent. Indeed in the 2021 ASRS international survey of ophthalmologists, 41% of US based ophthalmologists and 25% of international ophthalmologists felt GA was the biggest cause of vision loss in people with nAMD. Only 15 and 24% of respondents respectively considered undertreatment with anti-VEGF was the main reason[11].

Indeed, the incidence of atrophy in anti-VEGF treated eyes is relatively frequent, with it being reported to be 13% in the CATT study at two years 29% in HARBOR at 2 years, and 30% at 2 years in the IVAN study[6,12-15]. One approach to try and limit the atrophy is to target underlying pathways that might be leading to cell death. In this regard, faricimab, with its dual action of having an anti-VEGF as well as having anti Angiopoietin 2 (Ang 2) activity might offer some ability to combat additional pathological pathways. In a mouse model of neovascularization, those being treated with an anti-VEGF and an anti-Ang 2 had less inflammation, fibrosis and vascular leakage than mice treated only with an anti-VEGF[16].

Retrospective analysis of studies such as CATT and IVAN trials in post hoc analysis all report suggestive evidence of a possible relationship, where less intravitreal anti-VEGF leads to less atrophy. In a subanalysis of the CATT and IVAN trials, comparison of patients treated with monthly and PRN administration showed that the average rate of atrophy development was lower in the PRN group compared to the monthly group and that the risk of developing atrophy was lower in the presence of subretinal fluid, (SRF) suggesting that extreme efforts to eliminate fluid could be abandoned[15, 17-19].

Whilst debate still continues as to the role the anti-VEGF treatment might have in the causation of atrophy, the best advice still remains to adequately treat the nAMD in the first instance[15]. However, evidence exists that help guide decision when treating nAMD in an attempt to limit the number of anti-VEGF treatments given.

When using a typical treat and extend protocol for nAMD at each visit the doctor must decide on the presence or not of disease activity. This is often determined by the presence of fluid, with any fluid being deemed to be indicative of ongoing anti-VEGF activity and as such the treatment interval should be shortened. However not all black spaces on the optical coherence tomography (OCT) are indicative of active VEGF driven fluid with examples of draping, SRF over pigment epithelial detachments and atrophic cysts being other explanations[20-22]. SRF can indeed be found in cases without any evidence of nAMD such as in pseudo-vitelliform lesions and it is important not to misdiagnose these cases so that people are not subjected to unnecessary intravitreal injections[20].

Even in cases of true nAMD, evidence for the View trials and the CATT trial reveals that there is not a good correlation between improvements in best corrected visual acuity (BCVA) outcomes and the presence of a dry retina[19,23]. Indeed, aiming for stable SRF might be a better endpoint of treatment than aiming to completely dry the retina. The CATT study reports that tolerating a small amount of SRF was associated with better VA and may result in less macular atrophy[19].

The FLUID study aimed to determine if there was any significant BCVA benefit with ranibizumab when administered to completely resolve both intra-retinal fluid (IRF) and SRF (intensive fluid management arm) compared to aiming to resolve all IRF whilst allowing SRF (relaxed fluid management arm)[24]. In FLUID the primary endpoint was the mean change in BCVA from baseline to Month 24, and the study revealed that the mean change in BCVA in the relaxed treatment arm was non-inferior to the Intensive treatment (non-inferiority margin < 5 letters). The proportion of patients with 6/12 or better BCVA was no different between treatment groups, nor was the proportion of patients with 6/60 or worse. Yet the proportion of patients with SRF at baseline who never resolve their SRF was numerically more in the relaxed group, as

expected, given the protocol differences between group. These results were achieved with significantly fewer ranibizumab injections in the arm tolerant to the SRF[24]. Thus the FLUID study revealed that even in the setting of known nAMD that is being treated, an amount of stable SRF can be tolerated without adverse outcomes. In the 2021 ASRS survey 52% US and 59% international ophthalmologists answered that they tolerate some SRF when treating nAMD[11].

To gain an insight into how anti-VEGF treatment is being used in the real world and the outcomes, real world studies provide important data. The Voyager study is a real world outcome study looking at faricimab use for both nAMD and diabetic macular odema (DMO)[25]. However, the new insights provided will be valuable across all anti-VEGF treatments. For example, one aim of Voyager is to understand the many factors that potentially contribute to the disparities in outcomes with anti-VEGFs in the real world, which will be relevant across all treatments. Some of the factors being considered in Voyager are the adequacy of treatment frequency, the difference in how clinicians interpret disease activity and implement treatment and the impact of a greater diversity in patient populations in clinical practice when compared to trials. Whilst determining the long-term effectiveness and safety of faricimab in nAMD and DMO in the real-world setting, Voyager will also gain insights into real-world treatment patterns and factors driving clinician treatment decisions. Unlike other real-world studies Voyager has the ability to gather the imaging done in routine clinical practise to validate key anatomical features that influence visual outcomes. Uniquely, Voyager also provides a novel investigator interface that allows health care providers to gain a complete picture of the individual's patient journal with treatment, on one computer screen, with the aim of providing all the relevant information, summarized on one graph, to optimise individual treatment decisions. Voyager will follow up to 5000 patients for up to 5 years, in multiple sites and countries across the global, with the last patient visit expected in 2027, to allow for the collection of long-term data. This data will help address existing evidence gaps regarding why real-world outcomes with anti-VEGFs are generally poorer than those in clinical trials and provide insight into how to close this gap[25].

## Geographic atrophy

GA is the other late stage of AMD, which until very recently had no proven treatment to slow or stop its progression. It has traditionally been defined on colour fundus photography as a pale, well demarcated lesion with a choroidal vessel visible in its base. More recently fundus auto-fluorescent (FAF) imaging has been used to define the extent of GA for clinical trials, where it is defined as a black hypo-FAF lesion with sharp borders and has a corresponding hypo-pigmented lesion on colour photography. Using FAF images allows an accurate determination of the extent of a GA lesion, and as such can be used to determine the change in area of atrophy over time. The rate of change in the GA areas defined on FAF imaging has been the primary endpoint for many of the previous and current clinical trials aiming to find an effective intervention or GA.

Recently two new GA treatments have been approved by the food and drug authority (FDA) for use in the US which aim to slow sown the rate of growth of the GA lesions. The first approved intervention was pegcetacoplan, a complement factor 3 inhibitor, given by intravitreal in injection. When having injections either every month or every other month for 24 m there was a statistically significant slowing of the growth rate in GA of between 16-22% in the two pivotal trials – Oaks and Derby[26]. The efficacy appears greater in those with non subfoveal lesions compared to those under the fovea. Similar results were seen for the Gather 2 trial which investigated avacincaptad pegol, a complement factor 5 inhibitor[27]. At 12 months, there was a 17% reduction in rate of growth in those receiving intravitreal monthly ACP compared to sham. As a result of these pivotal studies the FDA approved their use in GA. Many other novel interventions, with most also targeting the complement pathway are well advanced and currently in clinical trials.

## Intervening in iAMD

With the first trials showing efficacy of treatments for GA, and many more in late-stage clinical trial development, it is possible that we are not that far away from having safe treatments that could potentially be used earlier in the disease process than has been the case in the current GA trials. Current trials have require a significant amount of atrophy to be present to satisfy the inclusion criteria. However, when treatments become less invasive, with reduced treatment burden and cost, it would be desirable to start earlier before central vision is threatened.

One of the significant challenges in demonstrating efficacy for any treatment that starts at an earlier time point in AMD is being able to plan a feasible study that can be carried out over an acceptable time frame, but that is long enough to show a difference between treatment and sham arms of the study, given the slowly progressive nature of the disease. Being able to run

shorter studies than that which would currently be needed to show a change in growth rate of atrophy, would help make these early trials feasible.

With the advances seen in our ability to image the retina, it is becoming possible to more granularly determine progression over time in eyes with non-late stage disease (ie eyes with drusen). It is possible to see in eyes with large drusen there is a subset of eyes that already show the first signs of cell death – or atrophy. Nascent GA (nGA) is a term that describes early changes representative of cells death in the OCT and is defined by the presence of subsidence of the inner nuclear layer (INL) and outer plexiform layer (OPL) and/or the presence of a hyporeflective wedge-shaped band within the Henle's fiber layer[28]. These changes signify a very high risk of progressing to GA within a few years[29]. This sign of nGA could be used to recruit participants at high risk of progressing the endpoint of GA, or could itself serve as a surrogate endpoint for GA. One prospective longitudinal observational study of 280 eyes from 140 participants with bilateral large drusen and without nGA or late AMD at baseline., looked at progression rates. The proportion of eyes progressing from first detection of nGA to GA at 24 months was 38%, with this increasing to 56% at 36 months[29]. In eyes that developed nGA, there was a marked increased risk of progression to GA compared to eyes that did not develop nGA. (Adjusted Hazard Ratio = 78.1; 95% CI = 13.6 to 448.0; P<0.001) and the development of nGA explained 91% of the variance in the time to develop GA[29].

Further natural history studies in non-late AMD are needed to better determine the most robust biomarkers of disease risk and endpoint for clinical intervention studies. There are several ongoing AMD studies aiming to better understand the natural history of AMD. One study is the HONU study which is being conducted at a number of international sites and aims to evaluate high risk intermediate (iAMD) disease progression by analyzing the timeline and rates of conversion from baseline iAMD to more advanced atrophic AMD stages[30].

The LEAD study was a novel interventional randomized trial that sought to intervene early in AMD and use a novel combined endpoint of multi-model defined late-stage AMD that included traditional late-stage AMD (nAMD and GA) together with nGA[31]. This study investigated the potential of nanosecond laser (2RT®, NovaEye, Adelaide Australia), used in high risk iAMD cases, to slow progression to late AMD. In previous preclinical studies the nanosecond laser has been shown to selectively target the retinal pigment epithelium (RPE) and to not damage the neurosensory retina as was seen when conventional thermal lasers were used with the same aim in mind. In preclinical animal studies, it has also been shown that the nanosecond laser can reverse the increase in thickness in Bruch's membrane, which recapitulates changes seen in AMD[32]. Given the supportive preclinical data, the LEAD randomized trial in iAMD was conducted across 6 sites in Australia and Northern Ireland. LEAD was a randomized, sham-controlled trial with participants randomly assigned 1:1 to receive laser or sham treatment to the study eye at six-monthly intervals for 36 months[33]. 292 participants with bilateral large drusen participated in the study and the final analysis. Overall, no significant difference in progression rate with treatment was seen (P=0.122). However, a post hoc analysis was undertaken to determine if the treatment effect differed according to the presence of coexistent reticular pseudo-drusen (RPD) at baseline. This analysis was undertaken as knowledge around RPD impact appeared to indicate that the RPE in eyes with RPD maybe more profoundly dysfunctional and as such, these eyes might not be ideal candidates for this intervention. The nanosecond laser aims to destroy some RPE to encourage cell division to create new RPE cells or to rejuvenated existing cells. In this analysis there was a treatment effect whereby those without RD did better with a 4 fold reduced progression rate in participants without RPD at baseline with laser treatment compared to sham treatment, whilst those with RPD may have had greater progression. (~2.5 fold increased progression rate for participants with RPD that had the active laser treatment compared too sham). This LEAD study, for the first time revealed a different treatment effect in AMD eyes with RPD when compared to those without RPD. This is an important finding and should be considered when thinking about other potential interventions in AMD as the different sub-phenotypes may behave differently[31].

## Conclusion

We are now in an era where we can do more for patients with AMD than ever before and the future looks bright with many new interventions on the horizon. Unmet needs continue around the ability to reduce the onset of atrophy and fibrosis in nAMD. Tremendous progress has been made in our ability to tackle GA, which until recently has had no treatment options. However, the need for more effective treatments for GA remains. There is a real possibility that in the near future, we will be able to intervene before late-stage vision threatening disease is present but the need for appropriately designed and feasible trials will require a greater understanding of the natural history of AMD. This will allow us to take advantage of advances in imaging and other biomarkers to help inform trial

design. Finally different phenotypical features of AMD may well need to be considered when trying to develop the most appropriate intervention for each individual patient.

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