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Impact of residual retinal fluid on treatment outcomes in neovascular age-related macular degeneration

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ABSTRACT

Treatment decisions for neovascular age-related macular degeneration (nAMD) in the setting of individualised treatment regimens are adapted to disease activity. The main marker of disease activity and trigger for re-treatment with anti-vascular endothelial growth factor (anti-VEGF) agents is the presence of retinal fluid on optical coherence tomography (OCT). Recently, attention has focused on the impact of residual retinal fluid on nAMD management. Based on a literature review and the combined clinical experience of an international group of retinal specialists, this manuscript provides expert guidance on the treatment of nAMD according to fluid status and proposes an algorithm for determining when to administer anti-VEGF treatment according to residual fluid status. We explore the role of residual fluid in treatment decisions and outcomes in nAMD, taking into consideration fluid evaluation and, in particular, distinguishing between fluid in different anatomic compartments and at different stages during the treatment course. Current limitations to identifying and interpreting fluid on OCT, and the assumption that any residual retinal fluid reflects ongoing VEGF activity, are discussed.

INTRODUCTION

The management of neovascular age-related macular degeneration (nAMD) has been revolutionised by the introduction of anti-vascular endothelial growth factor (anti-VEGF) agents, which have the potential to improve vision and restore the macular architecture by resolving haemorrhage and fluid.[1–3] Visual acuity (VA) is usually the main outcome measure in randomised controlled trials (RCTs), but the absence of fluid on optical coherence tomography (OCT) is one of the most commonly used measures of treatment efficacy.[3–5] While fixed treatment regimens were used in the pivotal studies of anti-VEGF agents, more flexible, personalised treatment strategies have evolved, including as-needed (PRN) and treat-and-extend (T&E) regimens,[4 6–8] and treatment decisions are now adapted after assessing the patient's level of disease activity. Markers of disease activity include decreased VA, new occurrence of haemorrhage, and the presence of fluid and subretinal hyper-reflective material on OCT.[9] However, the presence of fluid on OCT is often the earliest indicator of disease activity and, as such, is the feature most commonly used to determine disease activity in clinical practice. Thus, fluid status is taken into consideration when making re-treatment management decisions and adjusting treatment intervals.[10] It should be noted that, although retinal fluid is currently the predominant imaging biomarker for macular neovascularisation (MNV) activity and, thus, re-treatment needs, additional OCT biomarkers, such as the presence of subretinal hyper-reflective material[9] and hyper-reflective foci,[11] are being investigated as further biomarkers that may need to be considered.

Fluid is detected on OCT as hyporeflective spaces separating the normal retinal architecture and causing thickening of retinal layers. Traditionally, these hyporeflective spaces have been interpreted as implying the presence of fluid and ongoing VEGF activity and have therefore been used as an activity biomarker (ie, of active MNV); consequently, the goal of individualised treatment has been resolution of hyporeflective spaces as seen on OCT.[3 4 7 8 12] The HARBOR[6] and CATT[4] studies defined OCT evidence of fluid in any compartment as a criterion for re-treatment with a PRN regimen—that is, subretinal fluid (SRF), intraretinal fluid (IRF) or sub-retinal pigment epithelium (sub-RPE) fluid, as in a pigment epithelial detachment (PED). In contrast, the IVAN trial used only the presence of SRF or increasing IRF as signs of MNV relapse/reactivation to trigger treatment in the discontinuous treatment arms.[13 14] The FLUID study was a pioneer, advocating a tolerant approach towards small amounts of residual SRF, which is elaborated on later.[15] However, hyporeflective spaces are not always a surrogate for the accumulation of fluid from active MNV, as IRF can result from degenerative cysts in some cases, especially over areas of early atrophy, while SRF can be caused by non-exudative processes and does not necessarily imply the need for anti-VEGF treatment.[16] With these complexities in mind, it is interesting to note that in a recent American Society of Retina Specialists survey, more than 50% of participating physicians indicated that they would maintain treatment intervals and tolerate some recurrent extrafoveal SRF in recently diagnosed patients with nAMD.[17]

This review introduces an algorithm to guide the management of patients with nAMD according to residual fluid status. It provides expert recommendations for the assessment of fluid and describes the

predictive value of fluid in different retinal compartments for visual outcomes.

METHODS

This article is based on a review of the literature and a consensus among retinal experts from the Vision Academy, in collaboration with subject experts. The Vision Academy is a group of over 100 international experts who, through their collective expertise, provide consensus guidance for managing clinically challenging situations, especially in areas of controversy or with insufficient conclusive evidence (www.visionacademy.org). The Vision Academy is sponsored by Bayer.

Selected members of the Vision Academy met in 2019 to discuss the influence of fluid on treatment outcomes in nAMD, with a particular focus on the criteria for re-treatment with anti-VEGF therapy according to fluid status. For this review, the initial concept of exploring the impact of residual fluid on treatment outcomes in nAMD was first proposed to the Vision Academy membership in 2019 as an important topic for further investigation. Subsequently, the available literature published in the online PubMed database was reviewed. After discussion between the authors, a consensus was reached on the key factors that should be considered when evaluating and assessing retinal fluid and its impact on treatment decisions and outcomes, in particular, distinguishing between fluids in different anatomic compartments. Current limitations to identifying fluid on OCT were discussed, and the assumption that any residual retinal fluid reflects ongoing VEGF activity—and hence requires ongoing anti-VEGF treatment—was questioned. After re-evaluating the existing evidence to guide decisions for individualising treatment for nAMD, the authors applied the insights gained to develop an updated algorithm for determining when to alter anti-VEGF treatment protocols for nAMD according to residual fluid status. The algorithm was created for use in the clinic to guide fluid assessment and help clinicians form an educated opinion on the determination of disease activity, differentiate fluid in different compartments over the treatment course, drive adjustment of the treatment protocol as necessary and determine when treatment frequency can be adjusted according to disease activity.

The recommendations within the algorithm were developed by the authors and subsequently reviewed, commented on and endorsed by a majority of the Vision Academy membership. For each proposed recommendation, respondents were asked to rate their agreement according to the following options: ‘strongly agree’, ‘agree’, ‘neither agree nor disagree’, ‘disagree’ and ‘strongly disagree’. Responses from more than 50% of the Academy were required for the survey to be valid. To assess any influence of the healthcare system on the survey responses, respondents were also asked for the reimbursement status of treatment in their country of practice (ie, mostly reimbursed or mostly out of pocket). Biases were assessed using χ^2. Endorsement was established if 50% or more of respondents indicated that they agreed or strongly agreed with a recommendation. The list of Vision Academy members and mentees who contributed to the recommendations is provided at the end of the article.

DOES THE PRESENCE OF FLUID ON OCT EQUATE TO ONGOING VEGF ACTIVITY?

Clinical practice guidelines from the American Academy of Ophthalmology, the Royal College of Ophthalmologists in the UK, and the European Society of Retina Specialists state that fluid on OCT is an indication of active disease, and therefore recommend re-treatment when fluid is present.[13 18 19] In contrast, a ‘dry’ retina is believed to be a marker of absence of exudative activity. These assumptions are based on observations from RCTs of a clear correlation between the frequency of anti-VEGF injections and the absence of fluid. In studies with preplanned treatment-free periods, post-hoc analyses have captured a synchronised fluctuation in fluid, indicating active leakage.[20 21] In the VIEW studies, following the switch from a fixed regimen to a capped PRN regimen (mandatory dosing required at least every 12 weeks), a greater proportion of patients showed recurrent fluid, followed by a subsequent reduction in fluid after the first mandatory treatment.[20] Similarly, in the CATT study, fluid on OCT was more frequently seen in patients treated with a reactive PRN regimen versus those receiving monthly injections of ranibizumab (71% vs 53%).[4] Although the correlation between VEGF suppression and retinal fluid is evident, the assumption that any fluid in any retinal location is equivalent to ongoing VEGF activity, and therefore requires re-treatment, is being reconsidered. The idea that the presence of fluid at a single point in time is definitely indicative of MNV activity may not be so straightforward; this is also true of the dogma that requires even small amounts of residual MNV activity, as evidenced by fluid to be treated.

As the presence or absence of fluid is seen as the main indicator of VEGF activity in nAMD,[10] which plays into the management and decisions regarding re-treatment intervals, it is imperative that, if fluid does not resolve despite adequate treatment with anti-VEGF therapy, the original diagnosis is re-evaluated and a differential diagnosis for SRF considered, such as adult vitelliform macular dystrophy, central serous chorioretinopathy, optic disc pit maculopathy, Best disease, and others.[22] In these cases, the presence of SRF is not indicative of VEGF-driven neovascular disease activity.[23]

WHY DO WE NEED NOVEL WAYS OF ASSESSING THE PRESENCE AND QUANTITY OF FLUID?

Although RCTs often use an increase in central retinal macular thickness on OCT as a marker of disease activity, this only correlates weakly with the presence of fluid, due to the spatial distribution of fluid in different retinal compartments; while IRF is predominantly located in the central 1 mm macular area, SRF is predominantly located beyond this central area.[24] In a fully automated computational analysis that investigated the spatial correspondence between different fluid compartments, the authors reported spatial dissociation of SRF with IRF and PED, in contrast to co-localisation of IRF with PED.[25]

In the clinic, the presence of fluid is currently assessed on OCT in a manual, qualitative manner, and is therefore clinician- and imaging-dependent. Results from several RCTs conducted by experienced retina specialists highlight the limitations of this. While, in RCTs, reading centres report on the presence or absence of fluid seen on OCT per specific criteria in the study protocol, clinicians can arrive at a different interpretation of disease activity from the same scans, leading them to make different treatment decisions, based in part on their clinical experience, resulting in different treatment philosophies. This can lead to off-protocol decisions, impacting injection numbers and, ultimately, visual outcomes. In the CATT study, a review of OCT scans by the reading centre revealed that treatment decisions by study ophthalmologists were consistent with the re-treatment protocol in only 72%–74% of cases, with >90% of the discrepancies being related to fluid detection on OCT.[4] In the FLUID study, the reading centre and investigators differed in their assessment of IRF at baseline (assessed as present by 59%–64% vs 75%–80%, respectively).[26]

These discrepancies are likely due to clinicians adding their own clinical interpretations to the assessment of residual fluid, which then leads to different treatment decisions with different treatment burdens and, potentially, different treatment outcomes. Artificial intelligence (AI)-based algorithms may have great potential in this field, having been proven to be highly accurate in identifying different fluid compartments and providing quantitative topographic volumetric information.[24 25 27] A quantitative volumetric assessment of retinal fluid compartments in relation to visual function may complement the estimated central retinal thickness. Moreover, AI algorithms may add insight into the pathophysiological processes involved in the evolution of nAMD, identify disease patterns and correlate structure with visual function, thus enabling a more nuanced individualised treatment approach.[28] Nevertheless, there are current technical challenges to the application of AI that need to be addressed, such as in analysing patients with a tilted retina, possible segmentation errors and differences between OCT machines, as well as lack of real-time analysis and feedback. As AI-based algorithms continue to advance and become more widely implemented, practical guidance for assessing fluid status and adapting treatment decisions will continue to be needed to ensure optimal outcomes for patients. Even with an increased ability to detect fluid using AI, there is still a need to understand how the amount and location of the fluid, as well as other features, may help interpret its relevance to the VA outcomes of patients.

DOES THE PRESENCE OF FLUID IN DIFFERENT COMPARTMENTS PREDICT VISUAL OUTCOME?

To answer this question, it is essential to look at the different fluid compartments both at baseline and during the course of anti-VEGF treatment (induction and long-term follow-up).

Baseline OCT fluid status

The presence of fluid in different compartments at baseline has been found to impact VA outcomes in nAMD. The presence of SRF at baseline has been identified as a predictive factor for greater visual gains,[29–31] and 5-year results from the CATT study revealed that eyes without baseline SRF had worse visual outcomes and lost more vision than eyes with SRF.[32] In contrast, the presence of IRF at baseline is correlated with worse baseline VA and worse outcomes.[30 33 34] Patients with isolated SRF at baseline have been found to have numerically better baseline VA compared not only with patients with IRF, but also when compared with those with concomitant SRF or IRF.[35] Deep learning tools have demonstrated significant capability in automatically identifying, locating and quantifying fluid volume on OCT images.[27 28 36] Such algorithms have been applied to nAMD OCT scans to assess treatment response. A volumetric fluid analysis of the HARBOR data demonstrated a direct correlation between baseline best-corrected VA (BCVA) and fluid volumes: BCVA was reduced by 3.2 letters per 100 nL of foveal IRF. In contrast, baseline foveal SRF corresponded to a mean 6.5-letter improvement in BCVA per 100 nL fluid. However, baseline fluid volume had no statistically significant impact on the BCVA trajectory after month 1.[37]

Fluid status at baseline has been found to impact the need for re-treatment. In the EXCITE study, patients with baseline SRF achieved comparable visual gains regardless of whether they received monthly or quarterly injections of anti-VEGF therapy, indicating that, in these patients, less intensive treatment may be sufficient.[31] In contrast, patients without baseline SRF experienced significantly less visual improvement when treated with quarterly versus monthly injections.[31]

Change in fluid status under anti-VEGF treatment

Persistence of fluid is believed to be associated with ongoing MNV activity, implying that achievement of a dry retina would lead to better outcomes. However, the presence and type of fluid should be viewed in the larger contexts of time and its dynamic change under treatment. Therefore, it is important to characterise the behaviour of fluid under anti-VEGF suppression at different stages of treatment.

Induction phase

Although it is assumed that persistent fluid early in the treatment course adversely influences visual outcomes, the VIEW and CATT studies both found that persistent SRF had little impact on visual outcome, while patients with persistent IRF at 1 or 3 months experienced a reduction in VA after 1 year.[34]

In the CATT and VIEW studies, the greatest decreases in fluid and the greatest proportion of eyes reaching complete resolution of fluid were observed following the first injection, with further small decreases after the second and third injections, and plateauing thereafter.[4 34 38 39] It should be noted that SRF and IRF resolve differently. Several RCTs have shown that the IRF component diminishes to nearly its lowest level 1 week after the first injection, while SRF resolves more slowly and continually over 12 weeks.[20 21 40] These results were recently confirmed by an AI-based automated analysis of data from the HARBOR study, where IRF showed the greatest and fastest resolution, followed by SRF and finally, PED. After the induction dose of intravitreal anti-VEGF treatment, all fluid types reached their lowest levels[41]; hence, the correlation between retinal fluid and change in vision was greatest in this initial phase. An AI-based fluid analysis of the HARBOR data further demonstrated a direct correlation between BCVA response and fluid volumes: after the first injection, BCVA increased by 2.13 and 5.88 letters per 100 nL decrease in foveal IRF and SRF, respectively. Moreover, persistent IRF correlated with less VA improvement.[37]

In a retrospective study of nAMD, eyes with isolated SRF at baseline were found to have a smaller chance of complete fluid resolution after three induction doses, compared with eyes that had IRF or a combination of both SRF and IRF at baseline (22% vs 33% and 31%, respectively).[35] Interestingly, with ranibizumab 0.3 or 0.5 mg, the resolution of SRF has been reported to be dose-dependent, while no difference was found for IRF resolution.[21] Additionally, in a post-hoc analysis of the VIEW studies, aflibercept was shown to be more effective than ranibizumab in achieving early resolution of SRF (70% vs 59% at week 12).[20] In the HAWK and HARRIER trials, anatomic retinal fluid outcomes favoured treatment with 6 mg brolucizumab over treatment with 2 mg aflibercept at week 16 (34% of eyes treated with brolucizumab vs 52% of eyes treated with aflibercept in the HAWK trial, and 29% of eyes treated with brolucizumab vs 45% of eyes treated with aflibercept in the HARRIER trial, had IRF/SRF).[5]

Long-term follow-up

RCTs have shown that, despite strict and intensive injection protocols, the majority of patients still show retinal fluid over time. However, the mere presence or absence of fluid itself does not always translate to visual outcomes. While the CATT and VIEW trials reported different proportions of patients with a dry retina in the different treatment arms (ranibizumab, bevacizumab and aflibercept), there were no significant differences

in improvement in BCVA or prevention of vision loss over 2 years.[3 4 42] A post-hoc analysis of the CATT data used a different approach, looking at eyes with predominantly persistent IRF and SRF through week 12, year 1 and year 2. Predominantly persistent fluid was defined as the presence of the respective fluid type at baseline and in ≥80% of follow-up visits.[43] In 29.8% and 26.1% of eyes, predominantly persistent IRF was present through years 1 and 2, respectively, and was associated with a higher 2-year risk of scar development.[44] On the other hand, SRF persisted in 23.2% and 19.0% of eyes through years 1 and 2, respectively, and VA outcomes were similar to those without predominantly persistent SRF, after adjustment for baseline covariates and persistent IRF.[43]

In the SEVEN-UP study, 68% of eyes showed SRF and/or IRF after 7 years.[45] Contrary to expectations, dye leakage on fluorescein angiography was seen in only a small proportion of these patients, suggesting that persistent fluid in the long-term disease course is not necessarily the result of active leaking MNV (ie, its presence does not necessarily reflect ongoing VEGF activity).[42] The presence of persistent fluid does not seem to have a detrimental impact on vision over time, with poor visual outcomes being associated with the development of atrophy and scarring rather than with incomplete treatment of VEGF-driven MNV activity.[45] In a T&E setting, new occurrence of any fluid on OCT was shown to be likely to lead to vision loss, but small amounts of persistent fluid were tolerated without compromising vision.[46]

Results from the EXCITE study support the hypothesis that recurrent SRF does not necessarily reflect ongoing VEGF activity, as, surprisingly, eyes treated with quarterly injections of ranibizumab showed lower SRF levels than those receiving monthly injections.[21]

Although the presence or absence of fluid graded as 'overall dry' or not does not alter visual results, analysis by anatomic location of fluid compartments reveals significant differences. In an AI-based post-hoc analysis of the HARBOR trial, fluid volumes were quantified at all patient visits and localised in relation to the fovea. Across all study visits, IRF had a consistently negative impact on visual outcomes, while SRF had a weak positive impact. Beyond simply the presence of IRF, a 100 nL increase in IRF volume was associated with a loss of four BCVA letters.[41] It should be noted that, while this may well be a sign of ongoing disease activity, non-resolving hyporeflective spaces could also indicate outer retinal tubulations, and fluid detection algorithms still lack the ability to interpret the nature of the detected 'fluid'. Therefore, clinicians should consider the development of atrophic cysts as an explanation for the failure of hyporeflective spaces to resolve and benefit from anti-VEGF treatment.

A more recent post-hoc analysis of HARBOR data adds strong evidence that a dry retina does not automatically result in improved visual outcomes, showing that patients with residual SRF and no IRF at months 12 and 24 gained more vision than those with complete SRF resolution. Patients with both SRF and IRF that resolved had the second-largest vision gain, with patients who had residual SRF and IRF having the third-largest amount of vision gain.[47] These results support previous findings indicating that long-term persistence of IRF seems to negatively affect visual outcomes, while persistent SRF may be tolerated without worsening vision.[20 24 33 38 48 49] However, in the HARBOR analysis, only small changes in IRF volumes were noted during the maintenance phase, and subsequent BCVA changes were minor.[47] The variability in individual vision is therefore likely associated with other, non-assessed, retinal morphological changes.

Chakravarthy *et al* used AI analytics to characterise retinal fluid volume changes over time in different tissue compartments of the macula and demonstrated an adverse relationship between repeated cycles of fluid fluctuations and quiescence and visual outcomes.[50] These data indicate the importance of optimal management during the maintenance phase to avoid volume fluctuations over time.

A treatment-agnostic post-hoc analysis of the HAWK and HARRIER trials, which compared brolucizumab to aflibercept in patients with nAMD, found that the absence of retinal fluid at more visits after loading doses (weeks 12–96) was positively associated with visual outcomes, regardless of whether the fluid was intraretinal, subretinal or both.[51] As these results differ from those of previous studies, further exploration of the impact of the presence and quantity of fluid in different compartments is needed. A deep learning analysis[52] allowed for a treatment-agnostic correlation of fluid volumes with BCVA over this maintenance phase, and confirmed that lower volumes of any fluid type (IRF, SRF or PED) were associated with better visual outcomes. In addition to IRF, larger residual SRF and PED volumes were also associated with progressive vision loss over the duration of the study.[52]

IS MACULAR ATROPHY LINKED TO FLUID STATUS?

Macular atrophy is a common cause of reduced vision in the medium to long term, following initial short-term visual gains in nAMD.[53 54] Treatment regimens that aim to completely dry the macula often involve more frequent anti-VEGF injections.[26] Speculation over a possible association between injection frequency and atrophy continues. The CATT and SEVEN-UP studies reported an association between more frequent injections and the development of macular atrophy, as well as with the rate of atrophy enlargement.[53 55 56] On the other hand, the HARBOR and IVAN studies found no association between drug dose or frequency and macular atrophy.[54 57]

Several post-hoc analyses of RCTs have investigated the role of fluid in the different compartments in the development of macular atrophy. In the CATT and HARBOR studies, while baseline IRF was associated with macular atrophy development, the presence of baseline SRF was linked to a lower risk of developing atrophy versus no SRF at baseline.[54 56] Although the IVAN study did not find any relationship between baseline SRF and incident atrophy, residual SRF was linked to less macular atrophy development in some patients. Moreover, the area of intralesional atrophy was approximately one-third less when SRF was present compared with when it was absent.[57]

It has been hypothesised that fluid in the subretinal space may provide a protective barrier between the outer segments of photoreceptors and the pathological, possibly toxic, RPE. This hypothesis is supported by a 2019 study that showed topographic correspondence between ellipsoid zone integrity and fluid in different retinal compartments. Areas with SRF were more likely to exhibit intact photoreceptors, while resolution of SRF by month 12 was associated with decreased morphological photoreceptor integrity at the same timepoint.[58] A retrospective study supports these findings: eyes treated with a T&E regimen, with SRF as the sole manifestation of disease activity, exhibited rather low rates of macular atrophy during long-term follow-up.[59]

A real-world study that looked at the 10-year outcomes of patients undergoing anti-VEGF treatment found macular atrophy to be the most common cause of substantial vision decline.[60] However, patients with a continuous presence of SRF

had a lower proportion of atrophy after 10 years and a slower decline in VA than patients in whom the presence of SRF was not continuous throughout the entire 10-year period.[60] Even under prolonged VEGF suppression, persistence of flow within mature tangled vessels has been demonstrated in eyes with type 1 neovascular lesions.[61] Notably, the likelihood of developing geographic atrophy seemed to be reduced following long-term anti-VEGF treatment; this points to potential protective mechanisms, which might involve the supply of nutrients and oxygen, when SRF is present.[61] Still, in the long-term management of MNV, the role of SRF as a biomarker of neovascular disease activity requiring treatment needs further investigation.

IS THERE EVIDENCE TO SUPPORT DELIBERATE TOLERANCE OF FLUID?

Real-world studies of patients with nAMD have shown significantly worse visual outcomes than those reported in RCTs. One reason for this may be an insufficient number of clinic visits and undertreatment, which occur for a variety of reasons.[62–66] Poor compliance is often implicated, which contributes to VA decline and can result from: low adherence to a regimen of frequent injections, in some cases as a result of missed injections due to comorbidities; patient perception of the treatment administration, anxiety and discomfort; financial burden; and lack of transportation.[67]

To maintain initial gains from treatment on the one hand and reduce treatment burden on the other, re-treatment intervals may be adjusted according to the individual's MNV activity. As SRF and IRF appear to have different impacts on vision, a qualitative and quantitative assessment differentiating between fluids in different compartments and over time may offer a more reliable correlation with visual function.[47] In T&E regimens, physicians aim to individualise treatment based on the duration of response to anti-VEGF suppression, aiming to gradually extend the treatment interval while maintaining a dry retina.[8 68] The classical T&E algorithm dictates administering monthly injections until complete resolution of all IRF and SRF. If SRF persists despite maximal treatment intensity (ie, monthly treatments), traditional T&E protocols mandate no extension of the treatment interval. However, some physicians have suggested extending the injection interval in patients where there has been no further reduction in SRF or IRF on OCT for at least two consecutive visits in the absence of new retinal haemorrhage.[69] Data supporting a more tolerant re-treatment approach are available from the FLUID study, a randomised, phase IV clinical trial that introduced the novel approach of a 'relaxed' T&E regimen.[15] After an induction phase of 3 monthly injections, tolerance of residual SRF (unless it was >200 µm in height at the foveal centre) was found to be associated with visual outcomes comparable with those achieved with an intensive treatment that was 'intolerant' to any residual fluid, while requiring fewer injections over 2 years.[26] According to the methodology of the FLUID study, the assessment of residual fluid was qualitative (present or absent).

As discussed in the previous paragraph, IRF has a negative impact on visual outcomes,[20 33 47 48] therefore all treatment algorithms aim to achieve complete resolution of exudative intraretinal cysts. However, in patients with residual hyporeflective spaces despite intensive treatment, a thorough evaluation of OCT images is required to try and distinguish between actual IRF and optically empty hyporeflective spaces, which are often associated with OCT signs of atrophy,[70–72] or outer retinal tubulations that can be misdiagnosed as exudative intraretinal cystoid changes.[73 74] Nevertheless, to reiterate, it is the stability of the lesions, despite maximal treatment, that should alert to the possibility of fluid in a non-VEGF-driven environment, while new intraretinal cysts should raise suspicion of new VEGF-driven activity and should be managed accordingly.

In conclusion, retinal fluid that is indicative of ongoing disease activity, potentially from undertreatment, must be clearly distinguished from stable SRF that can be tolerated under a well-considered treatment regimen with strict follow-up. Post-hoc analyses from large RCTs have shown a correlation between residual SRF and better visual outcomes.[41 47] The recent phase III TENAYA and LUCERNE trials, which investigated faricimab (Vabysmo, Roche) in the treatment of nAMD, did not consider fluid as a criterion for disease activity but used central subfield thickness as the guiding anatomical parameter.[75] Hence, residual fluid might have been tolerated. Data from other large-scale RCTs using a 'relaxed' T&E approach to fluid tolerance are not yet available, and long-term follow-up data will be needed to evaluate the feasibility and efficacy of this approach in real life. Quantitative and qualitative assessments of fluid over time, combined with information on the drivers of physician decision-making on re-injections, could offer a better understanding of retinal fluid and its impact on visual outcomes. In this context, the ongoing VOYAGER study (NCT05476926) aims to collect real-world data to explore long-term effectiveness and safety, and it is also evaluating the presence and localisation of fluid, as well as the physician philosophy around fluid tolerance and injection protocols in patients receiving treatment for nAMD or diabetic macular oedema with faricimab or the Port Delivery System with ranibizumab in routine clinical practice.[76]

VISION ACADEMY RECOMMENDATIONS ON THE ROLE OF FLUID STATUS IN GUIDING TREATMENT OF NAMD

The recommendations listed in the figure were formulated by the authors of the manuscript and submitted to the entire Vision Academy membership for endorsement; 67 responses (including from the authors) were received. Overall, the recommendations were endorsed by 90% of the respondents (a response of 'agree' or 'strongly agree'), with the level of endorsement for each individual recommendation ranging from 79% to 97%. The mean (range) rate of non-endorsement was 5.2% (2%–14%) for a response of either 'disagree' or 'strongly disagree', and 4.8% (0%–12%) for a response of 'neither agree nor disagree' (figure 1). (It should be noted that these recommendations represent the ideal scenario, and full implementation may not be possible in all clinics.)

Diagnosis

A definitive diagnosis of active MNV (based on the previously discussed criteria) should be made prior to initiating treatment. Non-exudative MNV (ie, a neovascular membrane identified on OCT angiography, fluorescein angiography or indocyanine green angiography in the absence of IRF/SRF exudation[77]) should not be treated until there are signs of retinal fluid exudation. (While this recommendation was endorsed by the Vision Academy membership, a tendency was detected to disagree with this statement by those respondents practicing in healthcare environments where treatment costs are 'mostly out of pocket'.) The MNV lesion type, size and location in relation to the fovea should be established and recorded. The presence and localisation of fluid as seen on OCT should also be recorded at baseline (SRF/IRF/sub-RPE fluid).

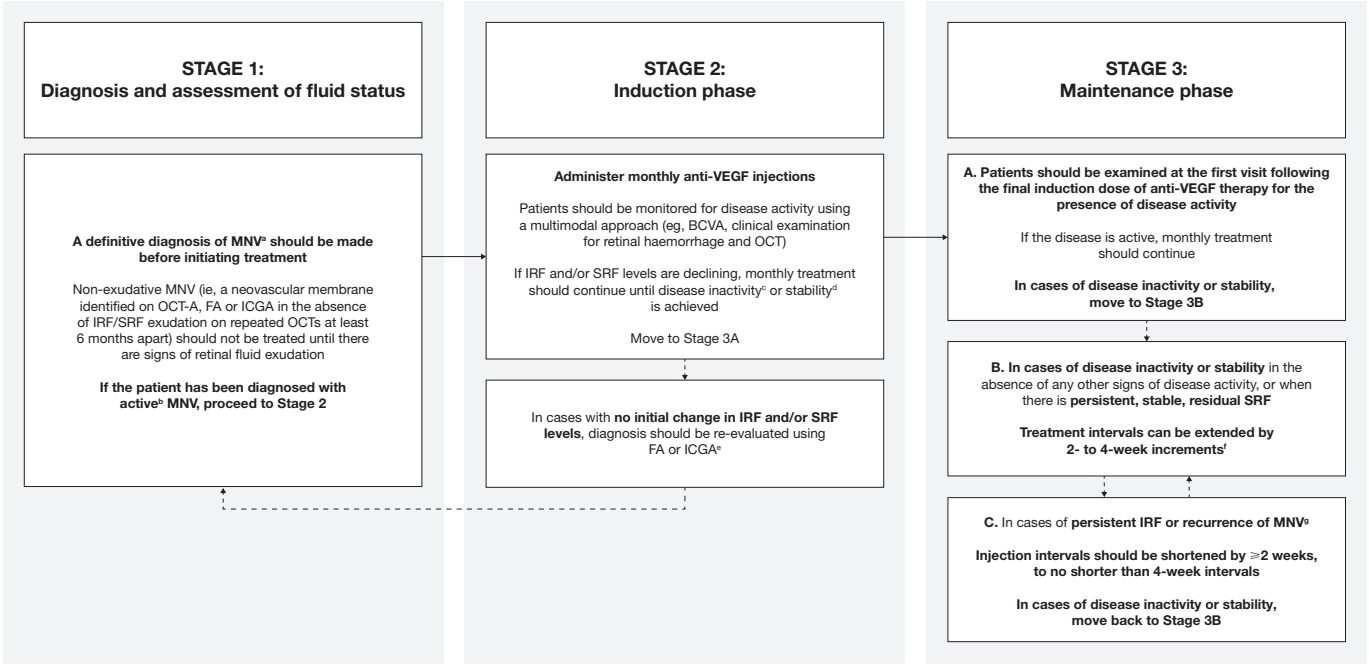

Figure 1 Recommendations on the role of fluid status in guiding treatment of nAMD. [a]The MNV lesion type, size and location in relation to the fovea should be established and recorded, and the presence and localisation of fluid as seen on OCT should be recorded at baseline. [b]Disease is considered active when the disease stability or disease inactivity states are not achieved, defined as: the presence of IRF and/or SRF attributable to VEGF activity, deterioration in vision attributable to MNV activity, presence of new retinal haemorrhage attributable to MNV activity, increasing amounts of SRF/IRF despite regular injections. [c]Disease inactivity is achieved when there is absence of IRF and SRF attributable to VEGF activity, absence of deterioration in vision attributable to MNV activity or absence of new retinal haemorrhage attributable to MNV activity. [d]Disease stability is achieved when there is no fluid or a small amount of persistent residual SRF without a further decrease, despite adequate regular injections being performed until maximal anatomic effect (with at least an initial three monthly injections during the induction phase), in the absence of any other signs of disease activity. [e]Hyporeflective cystoid spaces that are not responsive to anti-VEGF treatment should be re-evaluated for atrophic spaces, loss of tissue and outer retinal tubulations. [f]T&E is the regimen of choice. Treatment options should be discussed with the patient and an individualised treatment regimen offered. Treatment intervals should be extended at the physician's discretion. [g]Signs of MNV recurrence include any of the following: new retinal haemorrhage, vision deterioration, or new and/or increased IRF, SRF or sub-RPE fluid. BCVA, best-corrected visual acuity; FA, fluorescein angiography; ICGA, indocyanine green angiography; IRF, intraretinal fluid; MNV, macular neovascularisation; OCT, optical coherence tomography; OCT-A, OCT angiography; SRF, subretinal fluid; VEGF, vascular endothelial growth factor.

Definition of disease activity states (activity, inactivity and stability)

Ideally, disease activity should be evaluated at each visit, based on clinical examination and review of OCT images. A thorough evaluation of disease activity is crucial for determining the most appropriate treatment decision.

- Disease inactivity is achieved when there is:
  - Absence of IRF and SRF attributable to VEGF activity.
  - Absence of deterioration in vision attributable to MNV activity.
  - Absence of new retinal haemorrhage attributable to MNV activity.
- Disease stability is achieved when there is:
  - No fluid or a small amount of persistent residual SRF without a further decrease, despite adequate regular injections being performed until maximal anatomic effect (Based on the consensus among Vision Academy members, a small amount of persistent retinal fluid that is not decreasing despite adequate regular injections can be considered not attributable to VEGF activity. As the concept of fluid quantification is just emerging and prospective trials are still lacking, we chose not to indicate a specific amount of SRF, since this will be determined by future studies.) (with at least an initial three monthly injections during the induction phase).
  - In this case, and only in the absence of any other signs of disease activity, the disease can be considered stable, and the treatment interval maintained or cautiously increased.
- Disease is considered active when the aforementioned states are not achieved, that is:
  - Presence of IRF and/or SRF attributable to VEGF activity.
  - Deterioration in vision attributable to MNV activity.
  - Presence of new retinal haemorrhage attributable to MNV activity
  - Increasing amount of SRF/IRF despite regular injections.

Induction phase

The aim of anti-VEGF treatment in all patients with nAMD is to restore the retinal anatomy as soon as possible, by regressing MNV activity. Treatment should be given monthly during the induction phase and continued until the maximal anatomic effect is achieved.

- Patients should be monitored for disease activity through assessment of BCVA, clinical examinations for retinal haemorrhage and OCT imaging. The fluid compartments should be assessed individually, and fluid status should be evaluated to determine the appropriate treatment decisions.

- If IRF and/or SRF levels are declining, treatment intervals should be maintained until disease inactivity or stability is achieved.
- If there is no change in SRF or IRF levels initially, the diagnosis should be re-evaluated, with assessments including fluorescein or indocyanine green angiography. Hyporeflective cystoid spaces that are not responsive to anti-VEGF treatment should be re-evaluated for atrophic spaces, loss of tissue and outer retinal tubulations. Masquerading diagnoses for nAMD should be considered in cases where SRF does not change despite initial monthly injections (eg, acquired vitelliform lesions).

Maintenance phase

Patients should be examined at the first visit following the final induction dose of anti-VEGF therapy for the presence of disease activity. If the disease is active, monthly treatment should be continued. In cases of disease inactivity or stability, the treatment interval should be adjusted on an individual basis. Treatment options should be discussed with the patient and an individualised treatment regimen offered, with T&E being the regimen of choice. When a PRN approach is chosen, physicians need to make sure that monthly follow-up visits, with visual and OCT examinations, are feasible.

- ► In cases of disease inactivity or stability, the treatment interval can be extended by 2-week increments, or possibly up to 4-week increments, at the physician's discretion.
- ► When there is recurrence of MNV activity in any of the parameters (ie, new and/or increased IRF, SRF, or sub-RPE fluid, new retinal haemorrhage, or vision deterioration), injection intervals should be shortened by ≥2 weeks, to a minimum of a 4-week treatment interval, depending on the severity of the recurrence.
- ► Persistent VEGF-driven IRF is considered a biomarker of disease activity and should never be tolerated. The injection interval should be shortened by ≥2 weeks to no less than 4 weeks.
- ► A small amount of stable, residual SRF is considered compatible with favourable visual outcomes and can be tolerated. In these cases, treatment intervals can be cautiously extended in the absence of other signs of disease activity.
- ► Treatment intervals should be decreased if fluid volumes appear to increase.

CONCLUSIONS

This manuscript summarises the expert recommendations of the Vision Academy on fluid status guiding the treatment of nAMD. A treatment algorithm was developed to aid clinicians in the assessment of fluid status and in subsequent treatment decisions. Morphological retinal parameters on OCT are predictive of functional outcomes in nAMD, and RCTs show a strong relationship between VEGF suppression and reduction in OCT fluid. Nevertheless, the use of fluid-related signs and their interpretation as disease activity is ambiguous, and better markers of neovascular activity are needed. Despite intensive anti-VEGF treatment, a residual subretinal space may be seen after active exudation has ceased. Recent data indicate that vision outcomes when treatment intervals are extended while tolerating a small amount of SRF are non-inferior to those achieved when no SRF is permitted. Indeed, residual SRF does not negatively impact visual outcomes and has even been associated with greater vision gains. In contrast, IRF (which is exudative and not degenerative cysts) can be considered a biomarker of disease activity; IRF at baseline and its persistence under VEGF suppression are correlated with worse visual outcomes. Intensive treatment for IRF is therefore encouraged. Large-scale, long-term prospective studies using volumetric quantification of fluid in the different compartments, as well as documented presence of atrophic regions, would further clarify the role of residual fluid in the treatment algorithm for nAMD and, ultimately, in visual outcomes when treating patients with nAMD.

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