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VISION ACADEMY VIEWPOINT

The Vision Academy is a partnership between Bayer and ophthalmic specialists, established with the aim of addressing key clinical challenges in the field of retinal diseases: www.visionacademy.org.

Impact of Residual Fluid on Treatment Outcomes in Neovascular Age-Related Macular Degeneration

Background

Individualized treatment regimens for neovascular age-related macular degeneration (nAMD) have been revolutionized by the introduction of anti-vascular endothelial growth factor (VEGF) agents.[1-3] The main marker of disease activity and trigger for re-treatment with anti-VEGF agents is the presence of retinal fluid on optical coherence tomography (OCT), which is detected as a hyporeflective space.[4-6] Traditionally, these hyporeflective spaces have been interpreted as implying the presence of fluid and ongoing VEGF activity and have therefore been used as a disease activity biomarker; consequently, the goal of individualized treatment has been the resolution of hyporeflective spaces as seen on OCT.[2,4,6-9]

A review of the literature and available evidence[6] was conducted to:

- Discuss the presence of residual retinal fluid as a marker of disease activity in nAMD
- Provide an overview for the role of residual retinal fluid on treatment outcomes in nAMD
- Introduce an algorithm to guide the management of patients with nAMD according to residual fluid status

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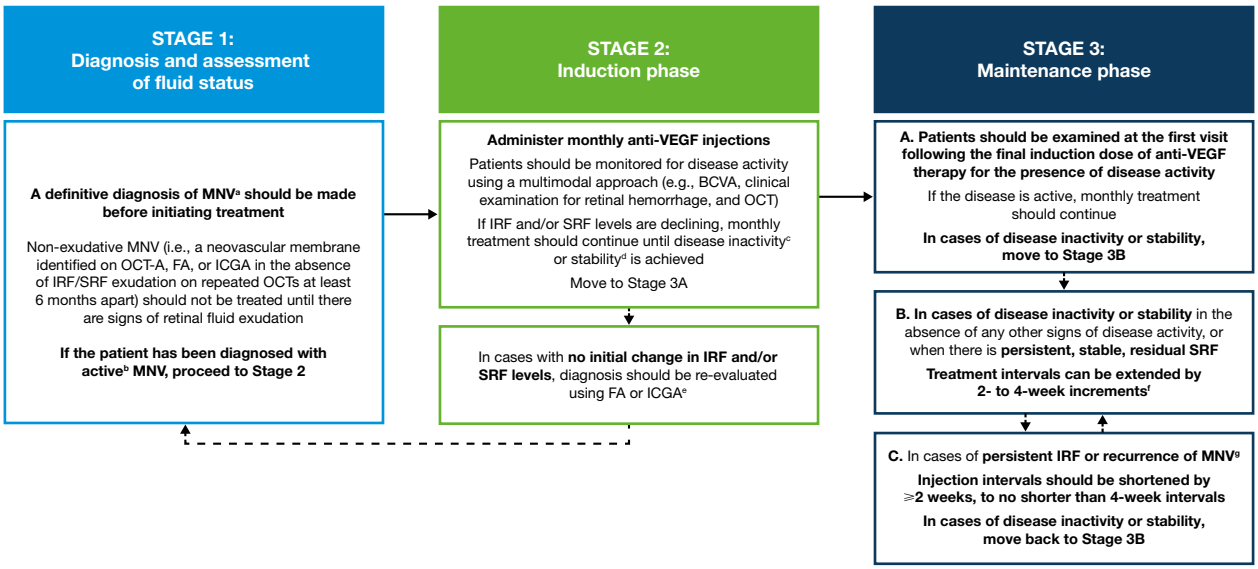
Viewpoint

After evaluating the existing evidence to guide decisions for individualizing treatment for nAMD, a set of recommendations and an algorithm were developed for determining when to adjust anti-VEGF treatment according to residual fluid status. This guidance was created for use in the clinic to direct 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 the adjustment of treatment as necessary, and determine when treatment frequency can be adapted to disease activity. The recommendations and algorithm were proposed by Zur et al[6] and subsequently reviewed, commented upon, and endorsed by a majority of the Vision Academy membership.

- A definitive diagnosis of macular neovascularization (MNV) should be made before initiating treatment. The presence and location of fluid on OCT, as well as the MNV lesion type, should be recorded at baseline
- Disease activity state should be assessed at each visit using a multimodal approach (best-corrected visual acuity [BCVA], clinical examinations for retinal hemorrhage, and OCT) and classified as active, inactive, or stable
- During the induction phase, fluid compartments should be assessed individually, and fluid status should be evaluated to determine appropriate treatment decisions. Monthly treatment should continue until disease inactivity or stability is achieved
- Patients should be examined at the first visit following the final induction dose of anti-VEGF therapy for the presence of disease activity
- During the maintenance phase, an individualized approach should be used to treat patients with inactive or stable disease, with a decrease in treatment intervals in the event of disease recurrence

Figure. Algorithm outlining recommendations on the role of fluid status in guiding the 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 localization 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 hemorrhage 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 hemorrhage 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 3 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]Treat-and-extend (T&E) is the regimen of choice. Treatment options should be discussed with the patient and an individualized 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 hemorrhage, visual deterioration, or new and/or increased IRF, SRF, or sub-retinal pigment epithelial fluid.

FA, fluorescein angiography; ICGA, indocyanine green angiography; IRF, intraretinal fluid; OCT-A, optical coherence tomography angiography; SRF, subretinal fluid.

Further considerations

Morphological retinal parameters on OCT are predictive of functional outcomes in nAMD, and randomized controlled trials have demonstrated a strong relationship between VEGF suppression and a reduction in retinal fluid. However, the use of fluid-related signs and their interpretation as disease activity remains ambiguous, highlighting the need for improved markers of neovascular activity.

Despite intensive anti-VEGF treatment, a residual subretinal space may be seen after active exudation has ceased. Data indicate that vision outcomes when treatment intervals are extended, while tolerating a small amount of subretinal fluid (SRF), are non-inferior to those achieved when no SRF is permitted.[10,11] Indeed, residual SRF does not negatively impact visual outcomes and has even been associated with greater vision gains. In contrast, intraretinal fluid (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 different compartments, along with the 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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