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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.

Management of Subfoveal Hemorrhage

Background

Subretinal hemorrhage is a manifestation of neovascular age-related macular degeneration (nAMD) in which blood from the retinal or choroidal circulation accumulates between the retinal pigment epithelium (RPE) and the neurosensory retina, causing severe visual impairment when the fovea is involved.[1]

Currently, there is a lack of evidence-based research and rigorous guidelines for the management of patients with subfoveal hemorrhage secondary to nAMD. In the past decade, a number of reports have demonstrated positive outcomes with a range of different treatments, including intravitreal anti-vascular endothelial growth factor (anti-VEGF), pneumatic displacement (PD), vitrectomy, intravitreal or subretinal tissue plasminogen activator (tPA), and various combinations thereof. Despite these, there remains a lack of consensus among vitreoretinal specialists on the optimal approach to managing patients with subfoveal hemorrhage.

This Viewpoint offers pragmatic clinical considerations and expert recommendations on defining, imaging, and treating subfoveal hemorrhage in nAMD.

Endorsed by the Vision Academy in May 2021.

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Full consensus Variations in opinion

Viewpoint

1. Definition

There is currently a lack of guidance on determining treatment of subfoveal hemorrhage based on size and thickness. Subretinal hemorrhages are often classified by size as follows:

- Small – measuring at least 1 disc diameter (DD) but smaller than 4 DDs[1]
- Medium – measuring at least 4 DDs but does not extend beyond the temporal vascular arcades[1]
- Large – extends beyond the temporal vascular arcades but not past the equator[2]
- Massive – extends past the equator in at least two quadrants[2,3]

'Thick' subfoveal hemorrhages (usually measuring >500 µm in thickness) are defined as blood under the fovea causing obvious elevation of the retina with obscuration of the RPE on fundus examination.[1,4] While many clinicians advocate the treatment of extrafoveal or 'thin' subfoveal hemorrhages with anti-VEGF monotherapy,[5] several studies have demonstrated poor visual outcomes with larger or thicker subfoveal hemorrhages.[3,6] However, these are becoming increasingly uncommon in clinical practice because of improved access to treatments at an earlier stage of hemorrhage manifestation.

2. Imaging

Color fundus photography, fundus autofluorescence, and spectral domain optical coherence tomography (OCT), including use of the enhanced-depth imaging mode, are important tools for localizing hemorrhage within the retinal layers to distinguish between subretinal and sub-RPE blood, and for objectively quantifying hemorrhage size.[1] While fluorescein angiography may be limited by the masking effect of subretinal blood, indocyanine green angiography (ICGA) may be a more useful method for hemorrhage visualization.[1] This may be especially true in populations where polypoidal choroidal vasculopathy (PCV) is highly prevalent because the infrared light employed in ICGA has a high penetration through RPE and blood.[1]

The Vision Academy recommends multimodal imaging with OCT to determine several prognostic factors for subfoveal hemorrhage, including hemorrhage size, thickness, and etiology, in order to drive treatment choice.[2,6-8]

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3. Treatment

Based on an extensive literature search, the Vision Academy made the following recommendations for the treatment of subfoveal hemorrhage in nAMD.

To minimize the risk of irreversible retinal damage, the Vision Academy recommends prompt initiation of anti-VEGF as a first-line treatment for subfoveal hemorrhage in nAMD, as well as in cases of PCV, in patients who are able to attend regular follow-up appointments. Careful monitoring with continued anti-VEGF treatment is important to minimize the risk of breakthrough hemorrhage and other complications. Further studies and large-scale randomized controlled trials are warranted to determine the full effects of hemorrhage duration on clinical outcomes with anti-VEGF therapy.

Most reports on anti-VEGF treatment of subfoveal hemorrhage in nAMD to date have come from non-randomized comparative studies or small, retrospective, uncontrolled case series reporting positive visual outcomes with anti-VEGF as monotherapy[9-11] and in combination with tPA, PD, and/or surgery.[12-16] Significant visual improvements seen in eyes with good baseline vision and short hemorrhage duration demonstrate the importance of early initiation of anti-VEGF treatment[9]; however, small sample sizes and differences in baseline features, inclusion criteria, and treatment regimens make it difficult to compare existing studies on anti-VEGF therapy.

The Vision Academy recommends intravitreal tPA with PD for medium, large, or thick subfoveal hemorrhages in patients with poor baseline vision (<20/200), at the discretion of the physician.

Evidence has demonstrated favorable visual outcomes with intravitreal tPA in combination with PD (both with and without vitrectomy) compared with PD alone for the treatment of subretinal hemorrhage.[17] While a sub-RPE hemorrhage in association with a subretinal hemorrhage involving the fovea does not preclude the use of PD or vitrectomy, the location and size of the sub-RPE component may affect the decision to perform these procedures.

The Vision Academy recommends surgical intervention only for severe subretinal hemorrhages, as determined by thickness and location. In all other cases, prompt anti-VEGF treatment and careful monitoring are recommended.

Evidence suggests that pars plana vitrectomy (PPV) in combination with subretinal tPA and PD may offer a more effective option than anti-VEGF monotherapy for the treatment of patients with thick or large hemorrhages and poor baseline vision.[4,11] However, without adequate prospective studies, it is not possible to draw comparisons between surgery and other treatment modalities because of likely variation in surgical techniques between reports.

Further considerations

One *in vitro* study assessed the anti-angiogenic activities of anti-VEGF agents when co-applied with tPA or plasmin, an enzyme that is liberated from the blood by tPA; when co-applied with plasmin at a concentration lower than the clinical dose, aflibercept was cleaved and its VEGF-binding ability reduced.[18] Inhibition of anti-angiogenic activity was not observed *in vitro* with aflibercept, ranibizumab, or bevacizumab when co-applied at clinical concentrations with plasmin,[18,19] nor with any of the three anti-VEGF molecules in a small retrospective case series of patients with submacular hemorrhage due to nAMD.[20] The TIGER study (NCT04663750), a Phase III, pan-European, observer-masked, superiority, randomized controlled trial, will assess the efficacy of anti-VEGF therapy alone versus with PPV in combination with subretinal tPA (n=210), and will provide valuable data to help support clinical decision-making.[21]

Regional variations in treatment reimbursement policies may affect treatment decisions. While economic factors often play a big role in determining treatment, the decision to perform surgery should be based primarily on clinical experience and consideration of the available evidence.

Vision Academy Viewpoints are intended to raise awareness of a clinical challenge within ophthalmology and provide an expert opinion to engage in further discussion.
They can be downloaded from https://www.visionacademy.org/resource-zone/resources/all
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