Title: The influence of vitreo-macular adhesion on outcomes following aflibercept therapy for neovascular age-related macular degeneration.

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Running head: PVD & aflibercept in AMD

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**Key words:** Vitreo-macular attachment, posterior vitreous detachment, aflibercept, age-related macular degeneration.

**Summary statement**: Although separation of the posterior hyaloid from the macula was associated with better anatomical and functional outcomes after intra-vitreal aflibercept for NvAMD when compared to eyes with persistent attachment, this failed to reach statistical significance.

**Abstract**

Purpose: To evaluate the influence of vitreo-macular attachment on outcome following intra-vitreal aflibercept for neovascular ARMD.

Methods: In a prospective, case series, eyes with neovascular ARMD were treated with intra-vitreal aflibercept, given as 3 consecutive monthly injections, followed by further injection every 2 months. Spectral domain OCT images were reviewed at each visit to determine the attachment of the posterior hyaloid. Best-corrected visual acuity and retinal thickness were also recorded. Outcomes at months were compared between the eyes with persistent vitreo-macular attachment (stage 1) and those with posterior vitreous detachment (stages 2 or 3 PVD) at baseline.

Results: At baseline, 30 eyes had stage 1 PVD and 63 eyes had either stage 2 or 3 PVD. Although there was a trend for both greater visual acuity gains and reductions in retinal thickness for the eyes with stages 2 or 3 PVD, this failed to reach significance. Baseline visual acuity and age were negatively associated with visual acuity change and baseline retinal thickness alone was associated with retinal thickness change.

Conclusions: Visual acuity, retinal thickness and age at the baseline examination, but not PVD status, are associated with functional and anatomical outcomes following intra-vitreal aflibercept for neovascular ARMD.

**Introduction:** In early life, most eyes have complete adhesion of the posterior vitreous cortex and the internal limiting membrane. With age, liquefaction of the cortical vitreous and weakening of the vitreo-retinal adhesion initiate a chronic process of vitreous separation or detachment.[1](#_ENREF_1) This detachment usually begins in the peri-foveal region and is manifest as vitreo-macula attachment (VMA) on optical coherence tomography (OCT) imaging.[2](#_ENREF_2) In most cases, it proceeds slowly and in stages to involve detachment of the cortical vitreous from the macula, the optic nerve and multiple sites throughout the peripheral retina. The end stage of this process is complete posterior vitreous detachment (PVD). Incomplete vitreo-retinal separation can lead to anomalous PVD.[1](#_ENREF_1)

 Persistent vitreo-macular attachment may alter the risk of developing age-related macular degeneration (ARMD). In the CATT study, persistent VMA was one of several factors shown to be associated with reduced risk of geographic atrophy, compared to eyes with PVD.[3](#_ENREF_3) Several studies have suggested that persistent VMA is more common in patients with neovascular AMD than in those with non-exudative AMD and healthy controls.[4-6](#_ENREF_4) In patients with unilateral, neovascular AMD, complete PVD is more common in the unaffected eye.[7](#_ENREF_7) Persistent adhesion of the vitreous may also occur at the site of choroidal neovascularisation, suggesting a possible role for anomalous PVD in the development of neovascular AMD.[8-10](#_ENREF_8)

 Differences in the degree of separation of the posterior cortical vitreous may also influence the response to treatment with intra-vitreal therapies for neovascular ARMD. In a retrospective study of eyes treated with anti-vascular endothelial growth factor (VEGF) monotherapy, vitreo-retinal adherence at baseline and visual acuity were the only ophthalmic factors that were associated with non-responder status.[11](#_ENREF_11) Eyes without vitreo-macular adherence had approximately 40% of the risk of being non-responsive to treatment. In 2 retrospective reviews of patients in the EXCITE and MONT BLANC studies, eyes with PVD at baseline were shown to achieve comparable visual acuity gains with less intensive treatment, suggesting a beneficial effect of PVD.[12](#_ENREF_12), [13](#_ENREF_13) Compared to eyes with VMA, Uney reported that those with PVD at baseline were more likely to have gains of 10 or more letters when treated with a loading phase of 3 injections of either ranibizumab or bevacizumab, followed by *pro re nata (prn)* therapy.[14](#_ENREF_14) Lee also reported that eyes with persistent vitreo-macular attachment had a decrease in visual acuity during follow-up, compared to an increase in those with PVD.[15](#_ENREF_15)

 However, the studies reporting the potential impact of persistent VMA on response to intra-vitreal therapies were often retrospective, utilised different therapies or treatment strategies, often employed time domain OCT and did not exclude eyes with either epi-retinal membrane or vitreo-macular traction.[11](#_ENREF_11), [12](#_ENREF_12), [14](#_ENREF_14), [15](#_ENREF_15) Several reported a different response for functional and anatomical outcomes.[11](#_ENREF_11), [14](#_ENREF_14), [15](#_ENREF_15) As a result it is difficult to draw firm conclusions about the role of persistent VMA in the response to treatment with neovascular AMD and there is a need for more evidence. This is particularly relevant given the opportunities provided by the introduction of ocriplasmin (Jetrea®, Thrombogenics, Leuven, Belgium) as a licensed treatment for vitreo-retinal interface abnormalities.

**Methods:** In a prospective study, the influence of persistent VMA on visual and anatomical outcomes following intra-vitreal aflibercept (Eylea®, Bayer Pharma AG, Germany) for treatment naïve, neovascular ARMD was investigated. Key inclusion criteria included aged over 65, a new diagnosis of neovascular AMD (all lesion subtypes and locations), informed consent for treatment with intra-vitreal injection of aflibercept, minimum follow-up for 6 months. Key exclusion criteria included presence of significant epi-retinal membrane or vitreo-macular traction in the study eye on baseline OCT imaging, other ocular pathology judged likely to compromise visual acuity change with treatment, ocular surgery during the follow-up period of treatment. For patients with bilateral disease, only the first eye was included.

 The intention was to give 3 consecutive, monthly injections of aflibercept, followed by further injection every 2 months. As this study involved patients in a real-world setting, some patients did not attend for all scheduled visits and the planned treatment schedule was not always followed. Patients with more than 1 missed visit during the follow-up were excluded from the analysis. For those with only 1 missed visit, the last observation carried forward approach was used to impute missing values for visual acuity and retinal thickness.

 At each clinic visit, the best-corrected visual acuity was recorded, using an ETDRS chart at 2m, and spectral domain OCT imaging performed. The scanning protocol compromised a macular thickness map, centered on the fovea, with 19 \* 300 horizontal line scans and 6 \* 200 radial line scans, centered on the optic disc. (Each line scan had a resolution of 512 A scans per section and automated real-time tracking was turned on throughout the scan acquisition.) The central 1mm sub-field thickness was recorded from the macular thickness map at each visit, with manual correction of the automated segmentation lines as required. Using a combination of OCT imaging of the macula and the optic disc, the stage of vitreous detachment in the treated eye was graded as follows (Figure 1): Stage 0: The posterior hyaloid is in contact with the entire surface of the macula and the optic disc; Stage 1: A shallow detachment of the posterior hyaloid is seen in the macula but it remains attached over the fovea and at the optic disc; Stage 2: The posterior hyaloid has detached from the macula but remains attached at the optic disc; Stage 3: The posterior hyaloid has detached completely from the macula and the optic disc. When the posterior hyaloid was not seen on OCT imaging, a Wies ring had to be present on slit lamp examination in order to differentiate between stages 0 and 3.

 Descriptive statistics for the baseline characteristics are reported as mean (±SD) for continuous variables and as percentages for categorical variables. The changes in visual acuity and retinal thickness were compared between the eyes with persistent VMA (stages 0 and 1) and those with an incomplete PVD involving the macula alone or a complete PVD (stages 2 and 3 respectively). Baseline characteristics were compared using an independent groups t-test for continuous variables. Linear regression modeling (ANCOVA), with baseline characteristics and values included as co-variables, was used to investigate an association between posterior vitreous detachment and outcome. A p value <0.05 was considered statistically significant.

 The institutional review board confirmed that ethics committee approval was not required for this study.

**Results:** Data from 93 eyes from participants were included in the analysis. For the whole group at the baseline visit, prior to the start of treatment, the mean age was 79.1 years, 38 participants (40.9%) were male and the following lesions characteristics were recorded on fluorescein angiography: 20 classic only, 8 classic with occult and 65 occult only, comprising 52 with fibrovascular pigment epithelial detachment, 12 with retinal angiomatous proliferation and 1 with polypoidal choroidal vasculopathy. Mean ETDRS letter score for all participants was 55.4 letters (SD=12.2) and mean 1mm central retinal subfield thickness was 409.5μm (SD=107.1). Mean letter score change at the month 2 and month 6 visits was +6.1 (SD=9.9) and +6.5 (SD=12.5) letters respectively. Retinal thickness decreased by 136.4μm (SD=90.8) and 112.3μm (SD=97.6) at the month 2 and month 6 visits.

 At the baseline OCT examination, stage 0 PVD was observed in 0 eyes, stage 1 PVD was observed in 30 eyes (32.2%), stage 2 PVD was observed in 9 eyes (9.7%) and stage 3 PVD was observed in 54 eyes (58.1%). Age, sex, mean ETDRS letter score and 1mm ETDRS subfield retinal thickness values at the baseline examination are given in Table 1 for the participants with PVD stages 1-3. Participants with stage 2 or 3 PVD were older than those with stage 1 PVD (p=0.006). Mean baseline visual acuity and retinal thickness in the eyes with stage 1 PVD were not significantly different to the eyes with either stages 2 or 3 PVD (p=0.47 and 0.73 respectively).

 In accordance with the planned analysis, the changes in mean ETDRS letter score and 1mm ETDRS subfield retinal thickness from the baseline examination to the month 6 visit are given in table 2 and illustrated in figures 2 and 3 for the participants with stage 1 PVD and with either stages 2 or 3 PVD at the baseline examination. Better baseline acuity and increasing age were negatively associated with visual acuity change at both the month 2 and month 6 visits but there was no association with PVD status. Although the eyes with stages 2 or 3 PVD at baseline had better visual acuity gains at both the month 2 and month 6 visits, the effect was not significant (p=0.23 and 0.19 respectively). Increasing baseline retinal thickness was associated with a reduction in retinal thickness at both the month 2 and month visits but there was no effect of age or PVD status. Although there was a trend for a greater decrease in retinal thickness at both time points in the eyes with stages 2 or 3 PVD, this was not significant (p=0.16 and 0.11 respectively).

 The mean number of injections before the month 6 visit in the patients with stage 1 PVD was 4.8 (SD=0.7). Progression to stage 2 PVD before or at the month 6 visit was seen in 2 (6.7%) subjects. The mean number of injections before the month 6 visit in the patients with stage 2 or 3 PVD was 4.8 (SD=0.5). None of the patients with stage 2 PVD at baseline progressed to stage 3 PVD during the 6 month follow-up.

**Discussion:** In this study, there was a trend for better functional and anatomical outcomes in the eyes with stage 2 or 3 PVD at the baseline visit but the difference was not significant when compared to the eyes with stage 1 PVD. This suggests that the degree of attachment of the posterior hyaloid to the macula has little or no impact on outcomes following treatment with regular intra-vitreal injection of aflibercept. Baseline characteristics other than the status of the posterior hyaloid had an effect on outcome. Eyes with better baseline acuity and those from older participants had smaller visual acuity gains. Greater reductions in retinal thickness were seen in the eyes with thicker retinas at the baseline examination. The influence of these baseline characteristics has been reported previously.[16-18](#_ENREF_16)

 Other studies investigating the effect of the posterior hyaloid have found conflicting results. In a retrospective study of eyes with neovascular AMD, treated with either ranibizumab or bevacizumab, Uney reported that eyes with posterior vitreous detachment had better functional outcomes at all time points up to and beyond 12 months.[14](#_ENREF_14) For the eyes with vitreo-macular adhesion, there was a decrease in visual acuity after the month 6 visit. Although the difference in retinal thickness was not significant, there was a trend for smaller reductions in retinal thickness in the eyes with vitreous separation, despite the better visual acuity outcomes. Some of the difference in visual acuity may also be explained by the worse baseline acuity in the eyes with PVD at baseline. In another retrospective study, Lee reported that mean visual acuity deteriorated in the eyes with vitreo-macular adhesion but improved in those without.[15](#_ENREF_15) The baseline acuities were matched in the 2 groups. However, there was no apparent difference between the groups in terms of the anatomical response to treatment. In a retrospective review of cases from the MONT BLANC study, Waldstein reported that eyes with baseline PVD had smaller visual acuity gains at month 12 than eyes with persistent or released vitreo-macular attachment, following a fixed loading phase and then *prn* ranibizumab therapy. This was despite greater acuity gains after the loading phase of treatment. Again, there was no difference in anatomical response to treatment according to baseline PVD status. In contrast, Cho reported no difference in functional or anatomical outcomes and polyp regression between eyes with and without vitreo-macular attachment following anti-VEGF therapy for polypoidal choroidal vasculopathy.[19](#_ENREF_19)

 In this study, 68% of eyes had detachment of the vitreous from the macula or beyond at the baseline examination and only 32% had persistent attachment of the posterior hyaloid within the macula. These figures are consistent with the age of the study population and are similar to those reported in other studies.[12-14](#_ENREF_12) Persistent attachment of the posterior hyaloid may be more common in patients with AMD than age-matched controls.[4](#_ENREF_4) Among the eyes in this study with stage 1 PVD at baseline, progression to stage 2 or 3 PVD was rare, occurring in 6.7% before the month 6 examination. This incidence figure is lower than the 13-19% reported by other authors for release of vitreo-macular adhesion, possibly reflecting longer follow-up and the use of PRN ranibizumab as opposed to fixed dosing with aflibercept. [12-14](#_ENREF_12) Uney reported that release of vitreo-macular attachment was seen after a median of 6 intra-vitreal injections.[14](#_ENREF_14)

 It is unclear if the minority of patients with release of VMA responds differently to intra-vitreal therapy than those with persistent VMA. In a retrospective review of images from the EXCITE study, Mayr-Sponer reported that there was no difference in visual acuity change between quarterly and monthly ranibizumab therapy in the eyes with PVD at baseline.[12](#_ENREF_12) However, the gains in visual acuity were greater in all the eyes with vitreo-macular attachment at baseline with monthly compared to quarterly therapy and greatest in those with release of VMA. In a similar review of images from the MONT BLANC study, Waldstein reported no difference in visual acuity change between the eyes with persistent and released VMA following ranibizumab monotherapy.[13](#_ENREF_13) Compared to those with baseline PVD, eyes with persistent or released VMA had a greater number of intra-vitreal injections to achieve similar visual acuity gains.

 This study has a number of strengths. For all the eyes in this prospective series, the baseline features and initial outcomes following aflibercept therapy are comparable to those seen in the registry studies.[20](#_ENREF_20) Similarly the effects of baseline visual acuity, retinal thickness and age on the functional and anatomical responses to treatment have been described before. To our knowledge, this was the first study investigating the influence of persistent vitreo-macular attachment to employ spectral domain OCT and to exclude eyes with vitreo-macular traction or epi-retinal membrane at the start of treatment. The use of real-world patients is likely to make the results more applicable to other centres than data from clinical trials with selective eligibility criteria. However, this also meant that some scheduled visits were missed or planned injections were not given, according to the decision of the patient and clinician at the time. Follow-up was sometimes delayed by annual leave and clinic capacity, although the latter was the same for all subjects and is unlikely to have added any bias to the findings.

 Although there was a trend for greater gains in visual acuity and reductions in retinal thickness in eyes with posterior vitreous detachment across or beyond the macula, this trend did not reach statistical significance. The age of the participants and baseline visual acuity and retinal thickness were better predictors of outcome within the first 6 months of treatment.

**Legends**:

Figure 1: Spectral domain, line scan OCT images through the macula and optic disc to illustrate the classification of posterior vitreous detachment used in this study.

Figure 2: Change in mean letter score for the eyes with stage 1 PVD at the baseline examination and those with either stage 2 or 3 PVD.

Figure 3: Change in mean retinal thickness for the eyes with stage 1 PVD at the baseline examination and those with either stage 2 or 3 PVD.

Table 1: Baseline characteristics of the participants and the eyes included in the analysis.

Table 2: Functional and anatomical outcomes according to baseline PVD status.**References:**

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