Original Article

The role of posterior vitreous detachment on the efficacy of anti-vascular endothelial growth factor intravitreal injection for treatment of neovascular age-related macular degeneration

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Purpose: A prospective cohort study investigating the effect of posterior vitreous detachment (PVD) on the efficacy of intravitreal bevacizumab for exudative age-related macular degeneration (AMD), in view of evidence that the vitreoretinal interface impacts the severity of the disease. **Methods:** Treatment-naïve AMD eyes with (+) complete PVD and without (−) PVD on ultrasonography received three monthly and then pro re nata bevacizumab injections. Best-corrected visual acuity (BCVA) on Snellen charts and optical coherence tomography (OCT) findings were recorded for 12 months. Secondary analysis included PVD definition and group allocation according to OCT baseline scan. **Results:** Forty-one eyes of 34 patients met the inclusion criteria. At 12 months, median BCVA improved by 0.12 logMAR in the PVD+ group [interquartile range (IQR) −0.52, 0.03, $P = 0.140$] and remained the same in the PVD− group (IQR −0.12, 0.15, $P = 0.643$). Median central retinal thickness improved by 43.5 µm and 43 µm in the PVD+ (IQR −143, 3, $P = 0.016$) and PVD− group (IQR −90, −14, $P = 0.008$), respectively. All parameters were similar in the two groups at final follow up ($P > 0.05$). The secondary analysis included 32 eyes of 26 patients and showed no significant differences between the groups at the 12 months endpoint ($P > 0.05$). **Conclusion:** Our findings show no significant impact of PVD as assessed by ultrasound or by OCT on visual and anatomical outcomes in exudative AMD treated with bevacizumab.

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Age-related macular degeneration (AMD) is a leading cause of severe and irreversible visual loss in the elderly in the western world.[1,2] Anti-vascular endothelial growth factor (VEGF) agents are the gold standard in the treatment of exudative AMD, but the degree of response varies widely, with some patients not responding at all.[3,4] Current research focuses on identifying characteristics that may influence or even predict treatment responses, with the goal being to develop individualized treatment regimens. Several investigations employing genotyping have detected a number of high-risk alleles associated with poor response to anti-VEGF treatment.[5,6]

There has been increasing interest in the effect of the vitreomacular interface (VMI) configuration on AMD. The incidence of posterior vitreous detachment (PVD) was found to be higher in eyes with non-exudative AMD, whereas vitreomacular adhesion (VMA) and traction (VMT) were correlated more frequently with exudative AMD.[7,8] Based on these findings, it was postulated that PVD may protect against exudative AMD, while VMA may promote it. Lee and Koh findings, in a retrospective study in which a pro re nata (PRN) regimen was used, suggested that anti-VEGF treatment for exudative AMD may be less effective in eyes with VMA than in eyes without VMA.[9] These results were supported in a prospective trial in which the configuration of the VMI significantly affected visual outcomes and need for retreatment.[10] Mojana *et al.* conducted pars plana vitrectomy in eyes with VMA and choroidal neovascularization (CNV) that were poorly responsive to repeated anti-VEGF treatments. Their results showed improved visual acuity (VA) and reduced retinal thickness.[11] The aim of the current study was to evaluate whether the presence of PVD affects the functional and anatomic outcomes of treatment with bevacizumab in exudative AMD.

Methods

This prospective cohort study was approved by the Medical Center's Institutional Review Board and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants.

The study enrolled patients with treatment-naïve exudative AMD, confirmed by fluorescein angiography and optical coherence tomography (OCT), who were scheduled to receive intravitreal bevacizumab injections. Exclusion criteria

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included a history of treatment for AMD, such as verteporfin photodynamic therapy or prior intravitreal anti-VEGF therapy, intraocular surgery (except cataract extraction), and CNV due to any cause other than AMD. Patients' enrollment was conducted between January 2012 and June 2013, with a follow-up duration of 12 months for each participant. Data of patients who missed the 1-year endpoint follow-up visit or missed more than one follow up were excluded from the calculations.

PVD was detected by 10 MHz B-Mode ultrasound examination of the posterior segment of the eye (AvisoS, Quantel Medical, Clermont-Ferrand, France) prior to anti-VEGF treatment. All ultrasound examinations were conducted by one proficient ultrasonographer, who is also an experienced ophthalmologist, under topical anesthesia with the patient in a supine position. For adequate characterization of vitreoretinal relationship, vitreous movement was evaluated during saccadic motion of the patient's globe while holding the probe stationary (kinetic assessment). A high sensitivity high gain setting was defined. The studied eyes were categorized into incomplete, complete, or absence of PVD [Fig. 1]. In order to have two distinct study groups, eyes with incomplete PVD were excluded from our cohort. Each scan was evaluated by the physician who conducted the examination and then reviewed independently by a second blinded ophthalmologist, with a 100% agreement between the reviewers. For the secondary analysis, OCT baseline scans were used to re-determine the VMI configuration as complete or incomplete PVD or VMA. VMA was determined by the following findings: 1. evidence of perifoveal vitreous cortex detachment from the retinal surface 2. macular attachment of the vitreous cortex within a 3-mm radius of the fovea 3. no detectable change in foveal contour or underlying retinal tissues.[12] OCT scans were analyzed by two independent physicians, blinded to the VMI status determination by ultrasound. Eyes with a definition of incomplete PVD and/or with a discrepancy between reviewers were excluded from the analysis.

For the first 3 months, all the participants received intravitreal bevacizumab 1.25 mg/0.05 ml (Avastin, Genentech) injections once a month, followed by a PRN regimen. In cases of good response bevacizumab was continued, and in cases of non-response treatment was switched to ranibizumab 0.5 mg/0.05 ml (Lucentis, Genentech). Non-response was defined as <10% reduction in central retinal thickness (CRT) according to OCT examination or deterioration in VA of ≥1 Snellen line.[13,14] In Israel, bevacizumab is approved as a first-line treatment for AMD as an off-label drug. In cases of non-response, as described above, after 3 monthly injections of bevacizumab patients can be switched to ranibizumab or aflibercept if they have the appropriate insurance coverage.

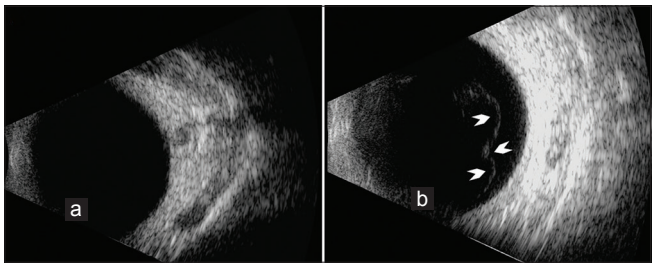

Figure 1: B-Mode ultrasound images of the posterior segment of (a) PVD– and (b) PVD+ eyes. Note the completely detached vitreous that appears as a wavelike membrane that moved freely away from the optic disc region during examination (arrowheads). PVD: Posterior vitreous detachment [with (+), without (–)]

Best-corrected visual acuity (BCVA) was measured with a Snellen chart at baseline and at 3, 6, and 12 months after the initial anti-VEGF treatment. The Snellen BCVA was converted to a logarithm of the minimum angle of resolution (logMAR) values for statistical analysis. Very low values on measures of VA, such as counting fingers, hand movements, light perception, and no light perception, were substituted by logMAR values of 1.85, 2.3, 2.6, and 2.9, respectively.[15,16] Data from OCT scans (Spectralis, Heidelberg Engineering, Heidelberg, Germany) were performed at baseline and 3, 6, and 12 months after the initial anti-VEGF treatment were extracted and used for this study. The treating physicians were eligible to choose injection frequency after the first 3 monthly injections, and their decision dictated the frequency of OCT scans and VA measurements, ranging from every month to every 3 months. In order to have comparable and complete data for this cohort we determined 3-monthly time points for BCVA and OCT follow ups. Measurements included CRT and maximal retinal thickness (MRT). The CRT and MRT were analyzed using the retinal thickness map analysis protocol, with 9 Early Treatment Diabetic Retinopathy Study (ETDRS) subfields. CRT was defined as an average retinal thickness of the circular area with 1 mm diameter around the foveal center. MRT was defined as the highest value subfield in the topographical map, excluding the fovea, at the baseline OCT scan. Measurements from that same subfield were recorded at the 3, 6, and 12 months follow-up scans [Fig. 2].

The primary outcomes were changes between baseline and follow-up values in BCVA, CRT, and MRT over 12 months. Secondary outcomes were the number of injections and the rate of treatment switching in the two groups over the 12 months.

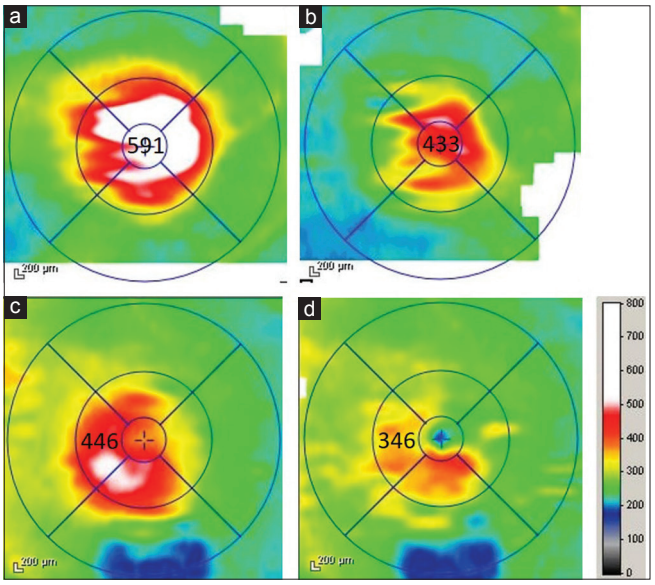

Figure 2: SD-OCT macular thickness maps at baseline and at the 12 months final scan. The diameters of the three rings are 1, 3, and 6 mm, respectively. Scans of (a and b) a right eye with PVD presenting a reduction of 158 μm in CRT, and (c and d) a left eye without PVD presenting a reduction of 100 μm in MRT, throughout the study follow-up. PVD: Posterior vitreous detachment; CRT: Central retinal thickness; MRT: Maximal retinal thickness; OCT: Optical coherence tomography

Statistical analysis

According to the power calculation, a minimum of 37 eyes were required to detect a difference of 5 letters with 80% power and within 95% confidence interval (CI) ($\alpha = 0.05$). Our data did not follow normal distribution and are therefore represented in medians and interquartile ranges (IQR). Differences were estimated using non-parametric methods; the Mann–Whitney U test, also known as the Wilcoxon rank-sum test for unpaired data and between group comparisons, and the Wilcoxon signed-rank test for paired data within groups. The level of statistical significance was set at $P < 0.05$. Data missing from the 3- or 6-month follow-up visits were imputed using the last observation carried forward (LOCF) method. Statistical analyses were performed with Microsoft Excel version 2007 (Microsoft Corporation, Redmond, WA), SPSS version 21 (SPSS, Inc., Chicago, IL) and Stata version 14.1 (StataCorp LP, College Station, TX) software.

Results

A total of 41 eyes of 34 patients (median age 82 years, IQR 73–87, 24 females, 10 males) who were scheduled to receive treatment with intravitreal bevacizumab injections for exudative AMD completed the study. Seven patients (17%) underwent treatment in both eyes. Seventeen eyes (42%) were pseudophakic. There were 22 eyes (54%) in the PVD+ group and 19 eyes (46%) in the PVD− group. The median baseline BCVA was 0.70 (IQR 0.4–1) logMAR and 0.52 (IQR 0.1–1) logMAR in the PVD+ and PVD− groups, respectively ($P = 0.242$). Baseline CRT and MRT median values were 353 µm (IQR 309–418) and 421 µm (IQR 375–491), respectively, for the PVD+ group; and 354 µm (IQR 305–429) and 446 µm (IQR 359–503), respectively, for the PVD− group ($P = 0.969$). There were no significant differences between the two groups with respect to age, gender, or lens status [Table 1].

Table 1: Baseline characteristics of patients with (+) and without (–) PVD

	PVD+ (*n*=22) % of total (number)	PVD– (*n*=19) % of total (number)	*P*
Eye			
Right	41% (9)	42% (8)	0.939
Left	59% (13)	58% (11)	
Age, years	82.5 (78-87)	80 (63-89)	0.538
Gender			
Male	27% (6)	32% (6)	0.765
Female	73% (16)	68% (13)	
Lens status			
Pseudophakic	61% (11)	35% (6)	0.132
Phakic	39% (7)	65% (11)	
Baseline BCVA, logMAR	0.70 (0.40-1)	0.52 (0.10-1)	0.242
Baseline CRT, µm	353 (309-418)	354 (305-429)	0.969
Baseline MRT, µm	421 (375-491)	446 (359-503)	0.969

All continuous data are median and interquartile range (IQR) PVD: Posterior vitreous detachment; BCVA: Best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; CRT: Central retinal thickness; MRT: Maximal retinal thickness

The paired comparison of the median BCVA values between baseline and 12 months showed a difference of 0.12 logMAR in the PVD+ group (IQR −0.52, 0.03) and no difference in the median logMAR in the PVD− group (IQR −0.12, 0.15) ($P = 0.140$ and $P = 0.643$, respectively) [Fig. 3]. However, the paired comparison between baseline and 6 months showed a significant median improvement of 0.08 logMAR only in the PVD+ group ($P = 0.034$). In this same group, the paired comparison between baseline and 12 months of the CRT and MRT values showed a significant difference of 43.5 µm in CRT (IQR −143, 3) and 81.5 µm in MRT (IQR −190, −30) ($P = 0.016$ and $P < 0.001$, respectively). In the PVD− group, the paired comparison between baseline and 12 months of the median CRT and MRT values showed a significant difference of 43 µm in CRT (IQR −90, −14) and 87 µm in MRT (IQR −156, −24) ($P = 0.008$ and $P = 0.001$, respectively) [Fig. 4a and b].

We then compared the two groups on the difference in median change between baseline and each follow up (baseline to 3, 6, and 12 months), as well as between two follow ups (3–6 months and 6–12 months). There were no significant differences between the PVD+ and PVD− groups in the extent of change in median BCVA, CRT, or MRT for any comparison period ($P > 0.05$). Nor were there any significant differences between the two groups in the actual values of BCVA, CRT, and MRT at 3, 6, and 12 months ($P > 0.05$) [Table 2].

The median number of injections during the 12 months was 6 for both the PVD+ and the PVD− groups ($P = 0.853$). Over one-fifth (22.5%) of the cohort was switched from bevacizumab injections to ranibizumab injections according to the criteria described above: 19% of the PVD+ group and 26% of the PVD− group, $P = 0.587$.

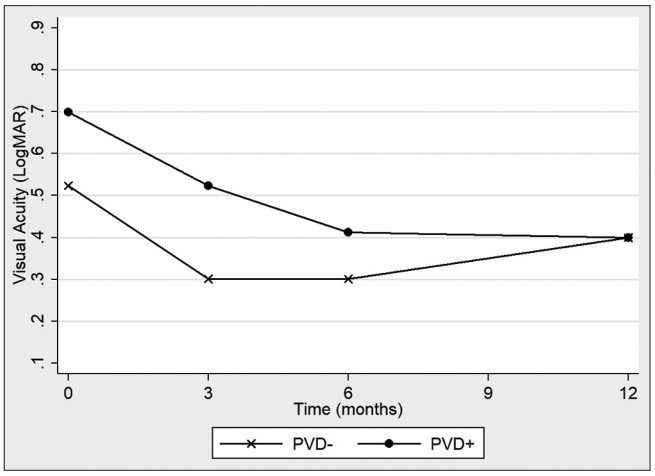

Figure 3: Change of median VA from baseline to 3, 6, and 12 months. The PVD− group had slightly better VA at baseline compared to the PVD+ group, and a moderate and gradual improvement over 12 months. The PVD+ group had a steeper improvement over time compared to the PVD− group, most prominent within the first 6 months of treatment. PVD: Posterior vitreous detachment [with (+), without (–)]; LogMAR: Logarithm of the minimum angle of resolution; VA: Visual acuity

The secondary analysis included 32 eyes of 26 patients, 20 eyes (62%) in the PVD+ group and 12 eyes (38%) in the VMA group. The reduced sample size stemmed from the exclusion of eyes with incomplete PVD. There were no significant

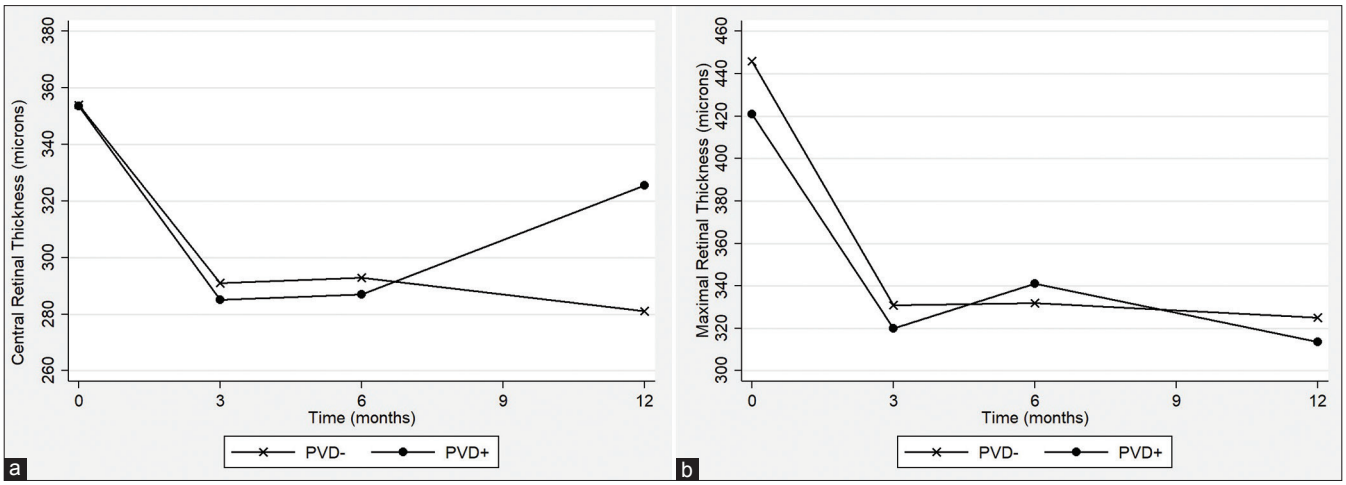

Figure 4: Change of (a) median CRT and (b) MRT between baseline and 3, 6, and 12 months. The PVD+ and PVD– groups had similar median CRT and MRT values at baseline and exhibited gradual improvement over time, most prominently during the first 3 months of treatment. The PVD– group reached lower MRT values and similar CRT values at 12 months compared to the PVD+ group ($P > 0.05$). PVD: posterior vitreous detachment [with (+), without (–)]; CRT: Central retinal thickness; MRT: Maximal retinal thickness

differences in baseline characteristics between the groups, and all of the endpoints primarily tested to compare between the groups were included in this analysis as well. There were no significant differences between the PVD+ and VMA groups in the extent of change in median BCVA or MRT in any comparison period ($P > 0.05$). With regards to the change in median CRT, the PVD+ group had a median of 55 µm greater decrease in CRT between baseline and 6 months follow up ($P = 0.028$), but there were no other significant differences between the groups in any other comparison. There were no significant differences between the two groups in the actual values of BCVA and CRT at 3, 6, and 12 months ($P > 0.05$). The PVD+ group had 53 µm and 40.5 µm lower MRT values at 3 and 6 months, respectively ($P = 0.031$ and $P = 0.034$, respectively), with no significant differences in MRT between the groups at the end of the study. We also performed a sensitivity analysis based on both the OCT and ultrasound determinations of PVD. Out of the 32 eyes appropriate for this analysis, we yielded 25 eyes of 21 patients whose OCT and ultrasound determinations of PVD were in agreement. The PVD+ group (15 eyes) and the PVD– group (10 eyes) reached similar results as shown for the primary analysis [Table 3].

Discussion

While there is abundant evidence that VMA and VMT are frequently correlated with exudative AMD, the effect of the VMI on anti-VEGF treatment in AMD remains unclear.[7,8,17,18] We found no significant differences in BCVA, retinal thickness, or number of injections for eyes with (+) and without (–) PVD.

Results from earlier studies on the impact of VMI configuration on treatment outcome are inconsistent. Our results are in agreement with those of a randomized multicenter trial that evaluated safety and efficacy of intravitreal ocriplasmin in patients with focal VMA and exudative AMD, and found no significant differences in visual outcome between eyes that developed PVD compared to those with VMA.[19] Our results are also in line with a prospective study by Kibbin *et al*. who found no association between PVD and functional and anatomical outcomes after aflibercept injections for exudative AMD.[20]

Table 2: Median changes in BCVA, CRT, and MRT from baseline to the 3-, 6-, or 12-month follow-up in patients with (+) and without (–) PVD

	PVD+	PVD–	*P*
BCVA, logMAR			
Baseline to 3 months	0 (–0.30, 0.08)	0 (–0.22, 0.08)	0.989
Baseline to 6 months	–0.08 (–0.52, 0)	–0.03 (–0.26, 0.05)	0.241
Baseline to 12 months	–0.12 (–0.52, 0.03)	0 (–0.12, 0.15)	0.233
CRT, µm			
Baseline to 3 months	–57.5 (–109, –9)	–33 (–94, –11)	0.814
Baseline to 6 months	–52 (–135, –6)	–45 (–90, –1)	0.574
Baseline to 12 months	–43.5 (–143, 3)	–43 (–90, –14)	0.917
MRT, µm			
Baseline to 3 months	–59.5 (–136, –29)	–54 (–144, –3)	0.734
Baseline to 6 months	–55 (–134, –37)	–62 (–163, –33)	0.804
Baseline to 12 months	–81.5 (–190, –30)	–87 (–156, –24)	0.824

All data are median and interquartile range (IQR) PVD: Posterior vitreous detachment; BCVA: Best-corrected visual acuity; logMAR: Logarithm of the minimum angle of resolution; CRT: Central retinal thickness; MRT: Maximal retinal thickness

However, a number of studies have also reported opposing results. The comparison of AMD treatment trial reported a trend for more intensive treatment in eyes with VMA/VMT compared to PVD, as did Houston *et al*. in a sub-analysis of the EXCITE study on the efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular AMD.[21,22] It is noteworthy that those studies used time–domain OCT, which

Table 3: Distribution of patients with (+) and without (–) PVD comparing ultrasound versus OCT determination

	Ultrasound determination		Total
	PVD+	PVD–	
OCT determination			
PVD+	15	4	20
VMA	3	10	12
Total	18	14	32

PVD: Posterior vitreous detachment; VMA: Vitreomacular adhesion; OCT: Optical coherence tomography

is limited by the lower image resolution. A retrospective study by Lee and Koh documented worse visual prognosis for eyes with VMA that were treated with anti-VEGF injections, without an effect on the number of injections needed.[9] Notably, the subjects in that study received a mean of only 3.66 injections in 12 months, which is below the accepted number of PRN treatments usually reported in clinical trials.[23,24] The MONT BLANC study also reported slightly better visual results for patients with PVD treated with ranibizumab monotherapy compared to ones with VMA.[25] Uney *et al*. described better visual outcomes for eyes with PVD compared to eyes with VMA; the vitreoretinal interface was evaluated in their patients by ultrasound and time–domain OCT, which is limited in displaying subtle VMA.[26] A recent meta-analysis covering 2212 subjects found better visual and anatomical outcomes, as well as fewer PRN injections required, in patients without VMT/VMA compared to those with VMT/VMA.[27]

Geck *et al*. have found that among eyes treated with intravitreal anti-VEGF injections for various underlying diseases including AMD, 24% had presented with a treatment-induced PVD during their follow-up period.[28] In our study the exposure status was exclusively determined by ultrasound prior to the treatment, without enabling transition during the follow-up period, since we emphasized our objective to investigate a factor that might predict the response to treatment and help in treatment tailoring. It is important to note that Geck *et al*.'s cohort was diagnosed and followed using a combination of fundus biomicroscopy, ultrasound and OCT and the level of concordance between the detection of PVD by these modalities varied, with only one patient who showed PVD in all methods. A number of studies that used OCT to determine VMI configurations referred to the presence or absence of VMA, but not PVD.[9,10,20–22,29] While VMA can be easily and accurately diagnosed by OCT, detection of PVD is limited. In cases in which complete vitreoretinal adhesion and complete PVD may not be distinguishable by OCT alone, ultrasound and biomicroscopy were found to be more reliable in the detection of PVD.[30] A retrospective study analyzing data from 130 pre-operative ocular ultrasounds performed by a single operator reported 96.2% sensitivity and 100% specificity for identifying posterior vitreous detachment.[31] In our study, we found an agreement between baseline OCT and ultrasound regarding the definition of PVD in 25 eyes (78%) as part of our sensitivity analysis, a rate that is relatively high compared to the current literature.[28,29] Our secondary analysis using OCT determination of the groups yielded almost the same results as the primary analysis. Although some minor differences between the groups were detected at several time points, these results did not hold at the 12 months follow-up examination and are probably representing transient changes between the groups that could be attributed to limited sample size. Along with the sensitivity analysis, we could not provide strong evidence against our primary analysis relying solely on ultrasound determination. Further research is needed to determine the optimal parameters for combining OCT and ultrasound to characterize the relationship between vitreoretinal configuration and treatment response.

There is a theoretical basis for assuming a correlation between PVD and treatment response to anti-VEGF agents. The state of the vitreous is related to the clearance, diffusion, and half-life of intravitreally injected drugs.[32,33] Evidence following microplasmin-induced PVD presents a significant decrease in the size of vitreous macromolecules and an improvement in the rate of oxygen exchange in the vitreous cavity due to increased oxygen levels. This support the hypothesis that PVD may alter the molecular flow in the vitreous and improve retinal penetration of drugs injected into the cavity.[34,35] However, two studies challenge this hypothesis: in one study, microplasmin-induced PVD in rabbits increased retinal penetration of bevacizumab only in the first 3 days; and in another study the intraocular pharmacokinetic properties of ranibizumab were similar in both vitrectomized and non-vitrectomized rabbit eyes.[36,37]

The contribution of VMA to treatment outcome has been studied for diseases other than AMD, including macular edema secondary to diabetes and retinal vein occlusion.[38,39] The results of those investigations were surprising: eyes with VMA had a greater potential for visual improvement than eyes without VMA. Although AMD and macular edema due to diabetes and retinal vein occlusion have different pathophysiologies, those results suggest that VMA alone, i.e. in the absence of retinal traction, may not adversely affect treatment outcomes.

The strength of this study is the prospective design that minimizes bias in the ascertainment of exposure, especially since PVD can occur following intravitreal injections as discussed above. One limitation of our study is the small sample size; although *a priori* sample size calculation postulated at least 5 letters difference between PVD+ and PVD− groups in order to reach significance, it is possible that the true difference in visual outcome is smaller and hence our sample was not able to demonstrate significant differences between the groups.

Conclusion

In conclusion, we found no difference in functional or anatomic outcomes related to the PVD status for eyes with exudative AMD treated with intravitreal bevacizumab. Further investigation with a larger sample and longer follow up is necessary in order to establish biomarkers that may point the way to patient-tailored treatment and optimal injection frequency.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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