# Impact of Vitreomacular Adhesion on Ranibizumab Mono- and Combination Therapy for Neovascular Age-Related Macular Degeneration

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• PURPOSE: To investigate the influence of vitreomacular adhesion on the efficacy of pro re nata (PRN) ranibizumab monotherapy and verteporfin photodynamic therapy (PDT) combination therapy for neovascular age-related macular degeneration.

• DESIGN: Post hoc analysis of prospective randomized 12-month multicenter clinical trial data.

• METHODS: <u>PATIENT POPULATION</u>: Total of 255 treatment-naïve patients with subfoveal choroidal neovascularization. <u>OBSERVATION PROCEDURE</u>: Assessment of the vitreomacular interface on monthly optical coherence tomography with division of patients into the following categories according to continuous 1-year grading: posterior vitreous detachment (n = 154), dynamic release of vitreomacular adhesion (n = 32), stable vitreomacular adhesion (n = 51). <u>MAIN OUTCOME MEASURES</u>: Mean best-corrected visual acuity (BCVA) letter and central retinal thickness changes at month 12 in the vitreomacular interface groups.

• RESULTS: Mean BCVA changes at month 12 were +3.5 (posterior vitreous detachment), +4.3 (release of vitreomacular adhesion), and +6.3 (vitreomacular adhesion) in patients receiving monotherapy (P = .767), and +0.1(posterior vitreous detachment), +6.6 (release of vitreomacular adhesion), and +9.2 (vitreomacular adhesion) in patients receiving combination therapy (P = .009). Mean central retinal thickness changes were  $-113 \ \mu m$ (posterior vitreous detachment),  $-89 \,\mu\text{m}$  (release of vitreomacular adhesion), and  $-122 \mu m$  (vitreomacular adhesion) in monotherapy (P = .725) and  $-121 \ \mu m$ (posterior vitreous detachment),  $-113 \mu m$  (release of vitreomacular adhesion), and  $-113 \mu m$  (vitreomacular adhesion) in combination therapy (P = .924). Mean ranibizumab retreatments during 12 months were 4.9 (posterior vitreous detachment), 6.6 (release of vitreomacular adhesion), and 5.3 (vitreomacular adhesion) in

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Inquiries to Christian Simader, Director, Vienna Reading Center, Department of Ophthalmology, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria; e-mail: optima@ meduniwien.ac.at monotherapy (P = .018) and 4.7 (posterior vitreous detachment), 5.2 (release of vitreomacular adhesion), and 5.8 (vitreomacular adhesion) in combination therapy (P = .942).

• CONCLUSION: This study adds evidence that the vitreomacular interface status impacts functional outcomes and retreatment requirements. Patients with posterior vitreous detachment achieve acceptable results with fewer injections in PRN monotherapy, but lose potential vision gain with PDT. Patients with other vitreomacular interface configurations may potentially achieve optimized vision outcomes by combination of antiangiogenic treatment and vaso-occlusive PDT. (Am J Ophthalmol 2014;158:328–336. © 2014 by Elsevier Inc. All rights reserved.)

NTRAVITREAL ADMINISTRATION OF ANTI-VASCULAR endothelial growth factor (anti-VEGF) agents is the current first-line therapy in the management of neovascular age-related macular degeneration (AMD).<sup>1</sup> Anti-VEGF agents effectively block the relevant signal cascade involved in the pathogenesis of choroidal neovascularization (CNV), leading to reduction of vascular leakage and restoration of visual acuity.<sup>2–4</sup> However, at the individual patient level, the magnitude and durability of the anatomic and, particularly, functional response to anti-VEGF therapy are markedly heterogeneous, which makes individualized dosing recommendations difficult. Despite meta-analysis of the Comparison of AMD Treatment Trials (CATT) and Inhibition of VEGF in Age-related Choroidal Neovascularisation (IVAN) trials suggesting inferiority of discontinuous pro re nata (PRN) vs continuous monthly treatment, most clinicians aim to treat patients as little as possible, but as much as required to control the chronic and progressive disease course.3-9 Moreover, treatment results in real-life scenarios usually fail to reach the level of vision improvement reported from clinical trials.<sup>10</sup> Although some microstructural characteristics that are predictive of treatment response have been identified, such as the presence of intraretinal cysts, the exact disease mechanisms responsible for individual response patterns are poorly understood.<sup>11</sup> Therefore, identification of reliable morphologic parameters that could successfully guide individualized treatment represents an unmet medical need.

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In this context, the condition of the vitreomacular interface is gaining scientific interest, while modern imaging strategies enhance the investigation of the vitreous itself.<sup>12–16</sup> Typically, patients in the AMD age group show a complete posterior vitreous detachment, defined as separation of the posterior vitreous cortex from the retina and liquefaction as well as anteposition of the vitreous body.<sup>17</sup> A minority of patients (20%–30%) present with persistent vitreomacular adhesion. As the vitreomacular interface configuration is a dynamic condition with potential transitions of one state to another, about 40% of patients with initial vitreomacular adhesion experience a release of vitreomacular adhesion and conversion to posterior vitreous detachment during several months of anti-VEGF treatment, although release may already occur after a single intravitreal injection.<sup>13,18,19</sup>

Several pilot studies reported an influence of vitreomacular interface configuration on treatment efficacy in anti-VEGF therapy for neovascular AMD, with less favorable outcomes for patients with vitreomacular adhesion.<sup>13,14,20</sup> The first large prospective study showed distinct response patterns of intravitreal ranibizumab in eyes with posterior vitreous detachment. Equivalence of monthly vs quarterly treatment was proven, as well as functional superiority of monthly vs quarterly treatment in patients with vitreomacular adhesion or dynamic vitreous release.<sup>21</sup>

Apart from anti-VEGF therapy, the other approved therapeutic approach to neovascular AMD is verteporfin photodynamic therapy (PDT).<sup>22,23</sup> PDT targets the neovascular lesion selectively via photochemical vaso-occlusion with minimal effect on neurosensory retina and adjacent structures,<sup>24,25</sup> and it remains the treatment of choice for selected subtypes of CNV, such as polypoidal choroidal vasculopathy, which is exceedingly frequent in Asian populations, and CNV secondary to central serous chorioretinopathy.<sup>26</sup> Since PDT itself triggers the release of VEGF and other pro-proliferative factors, the potential synergistic effect of PDT and anti-VEGF treatment in neovascular AMD provided the rationale for the largescale SUMMIT clinical trial program evaluating combination of PDT with ranibizumab therapy. However, these studies showed no benefit of combination therapy in terms of vision outcome and inconclusive results regarding a potential reduction in treatment frequency.<sup>27–29</sup> Nevertheless, recent studies reported a beneficial effect of PDT in recalcitrant cases of neovascular AMD, suggesting that—in addition to its role in the treatment of polypoidal choroidal vasculopathy-PDT may provide a useful therapeutic tool in selected AMD patients, and adding weight to the current concept of personalized therapy.<sup>30</sup>

This analysis focuses on a study based exclusively on a PRN regimen and compares the impact of the vitreomacular interface condition on anti-VEGF monotherapy vs combination therapy with PDT, with the aim to evaluate visual outcome and retreatment frequency. A standardized analysis of prospective multicenter trial data was conducted by an independent central reading center. Monthly optical coherence tomography (OCT) examinations were analyzed and correlated with vision response and retreatment rate.

# **METHODS**

THIS POST HOC ANALYSIS OF PROSPECTIVE MULTICENTER clinical trial data was conducted in compliance with the tenets of the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice guidelines. The ethics committee at the Medical University of Vienna, Austria, prospectively approved the current study. At each participating multicenter study site, prospective ethics committee or institutional review board approval was obtained. All patients provided written informed consent before enrollment into the trial. The study is registered at www.clinicaltrials.gov (NCT00433017).

• MONITORING AND TREATMENT PROTOCOL: All patients were participants of the MONT BLANC study, a randomized, single-masked multicenter phase II study in patients with primary subfoveal CNV secondary to AMD. Detailed information on trial design, inclusion and exclusion criteria, and primary as well as secondary outcomes have been published.<sup>27</sup> In brief, MONT BLANC was designed to compare the efficacy of ranibizumab (Lucentis; Genentech Inc, South San Francisco, California, USA) monotherapy vs combination therapy of ranibizumab and PDT. Patients were randomly assigned to receive either PRN combination treatment regimen (verteporfin PDT 6  $mg/m^2$  and ranibizumab 0.5 mg) (Arm 1) or PRN ranibizumab monotherapy (sham infusion [5% dextrose] PDT and ranibizumab 0.5 mg) (Arm 2). On day 1, verteporfin or sham infusion was followed by laser application at standard fluence (wavelength, 689 nm; irradiance, 600 mW/cm<sup>2</sup>) for 83 seconds (light dose, 50 J/cm<sup>2</sup>). Intravitreal ranibizumab 0.5 mg (10 mg/mL) was administered a minimum of 1 hour after the start of verteporfin PDT. Two consecutive ranibizumab injections were performed at months 1 and 2. After this loading phase, verteporfin PDT and ranibizumab were administered according to predefined retreatment criteria at intervals of 90 and 30 days, respectively, as described in detail previously.<sup>27</sup> Retreatment parameters included a 100  $\mu$ m increase in OCT-determined central retinal thickness from the lowest previous value, presence of subretinal fluid or new hemorrhage, best-corrected visual acuity (BCVA) decrease of 5 or more letters, and leakage on fluorescein angiogram.

All patients underwent standardized monthly monitoring according to protocol, including measurement of BCVA by certified examiners according to the Early Treatment Diabetic Retinopathy Study protocol, slit-lamp examination, and fundus biomicroscopy. At each visit, eyes were imaged by certified examiners using Stratus OCT (Carl Zeiss Meditec, Dublin, California, USA) after pupil dilation and before the administration of treatment. The scanning protocol included the typical standard scanning modi for clinical trials at the Vienna Reading Center and consisted of 1 "6-mm cross-hair scan" (2 sections perpendicular to each other with a resolution of 512 A-scans per section) and 1 "fast macular thickness map scan" (6 6-mm radial sections with a resolution of 128 A-scans per section) at each visit.

• EVALUATION OF THE VITREOMACULAR INTERFACE: Analysis of the vitreomacular interface was performed on raw, masked OCT datasets at the Vienna Reading Center using a validated grading scheme as reported in detail previously.<sup>21</sup> Briefly, trained and certified readers graded the vitreomacular interface configuration at each visit into 1 of the following states: (1) vitreous completely attached; (2) focal vitreomacular adhesion; (3) vitreous border antepositioned without contact to the macula; (4) vitreous border not visible. If vitreomacular traction was detected, the patient was excluded from further analysis since presence of vitreomacular traction was part of the MONT BLANC study exclusion criteria. The vitreomacular interface gradings from each visit were integrated after completion of the initial grading, and each patient was assigned to 1 of the following categories reflecting the vitreomacular interface configuration over the entire 12-month study period: (1) stable vitreomacular adhesion; (2) progressive release of vitreomacular adhesion; (3) posterior vitreous detachment. Representative grading examples for the 3 categories are provided in Figure 1.

• STATISTICAL ANALYSIS: Vitreomacular interface groups were compared by analysis of variance and  $\chi^2$  tests at baseline with respect to age, BCVA, central retinal thickness, intraretinal cysts, subretinal fluid, and pigment epithelial detachment, respectively. Further analyses were performed on differences to baseline. Differences after the loading phase and at the end of the first year were analyzed by 2-factor analysis of variance with vitreous groups and treatment groups as factors. Further differences were tested by linear contrasts. Corrections were made for multiple comparisons but not for multiple endpoints. *P* values less than .05 were considered statistically significant.

# RESULTS

• **PATIENT DISPOSITION:** Of the 255 patients included in the trial, 237 patients had complete vitreomacular interface data over 12 months available according to protocol. The ranibizumab monotherapy arm (n = 123) received a mean of 5.6 ranibizumab treatments following the loading



FIGURE 1. Grading examples for the 3 main vitreomacular interface configurations in study patients at baseline. (Top) Vitreomacular adhesion. The posterior vitreous boundary is focally adhering to the retinal surface between the 2 arrows. Arrowheads indicate areas of vitreous detachment. (Middle) Release of vitreomacular adhesion. In this case, the vitreous has separated from the macula. Further antepositioning of the vitreous boundary is, however, hindered by presumed attachment at the optic disc or retinal vessel arcades. In the current study, "release of vitreomacular adhesion" was also graded if a patient transitioned from vitreomacular adhesion to posterior vitreous detachment during the course of the trial. Arrowheads indicate areas of vitreous detachment. (Bottom) Posterior vitreous detachment. Antepositioning of the posterior vitreous cortex beyond the imaging range of the optical coherence tomography device precludes observation of vitreous structures; the space anterior to the retina appears optically empty. Posterior vitreous detachment was diagnosed only if vitreous structures were never visible throughout all observations of a particular patient over a 1-year time course.

dose. In the combination therapy arm (n = 114), a mean of 5.2 ranibizumab injections and 1.8 verteporfin PDT retreatments were administered during the PRN phase.

TABLE 1. Distribution of Patients by Vitreomacular Interface Configuration for Monotherapy and Combination Arms

	Posterior Vitreous Detachment $N = 154$	Vitreomacular Adhesion $N=51$	Release of Vitreomacular Adhesion $\label{eq:N} N = 32$	Total N = 237
Monotherapy, % (n)	64.2 (79)	21.1 (26)	14.6 (18)	100 (123)
Combination therapy, % (n)	65.8 (75)	21.9 (25)	12.3 (14)	100 (114)

TABLE 2. Baseline Characteristics in the Vitreomacular Interface Groups

	Posterior Vitreous Detachment			Vitreomacular Adhesion		Release of Vitreomacular Adhesio				
	Combination Therapy	Monotherapy	Р	Combination Therapy	Monotherapy	Р	Combination Therapy	Monotherapy	Р	Р
Age (mean ± SD)	77 ± 7.3			72 ± 8.0			76 ± 6.3			<.001
	$78\pm6.8$	$76\pm7.7$	.103	$71 \pm 9.0$	$73\pm6.9$	.474	$77\pm5.6$	$75\pm6.9$	.506	
Best-corrected visual	$55\pm12.8$			53 ± 10.8			57 ± 12.5			.494
acuity (mean $\pm$ SD)	$55 \pm 12.6$	54±13.0	.592	$54 \pm 12.4$	$52\pm9.1$	.570	$53 \pm 15.7$	$59\pm9.1$	.216	
Central retinal thickness	$338 \pm 119.8$			344 ± 102.2			$334 \pm 103.3$			.915
(mean $\pm$ SD)	$337\pm100.5$	$339 \pm 136.6$	.636	$325\pm86.7$	$363 \pm 114.3$	.244	$334\pm79.2$	$333\pm120.1$	.575	
Intraretinal cysts (%)	53.9			56.9			40.6			.314
	53.3	54.4	1.000	48.0	65.4	.264	35.7	44.4	.725	
Subretinal fluid (%)	57.8			68.6			75.0			.111
	64.0	51.9	.144	76.0	61.5	.368	71.4	77.8	.703	
Pigment epithelial	59.1			64.7			68.8			.520
detachment (%)	57.3	60.8	.744	68.0	61.5	.771	57.1	77.8	.267	

• VITREOMACULAR INTERFACE CHARACTERISTICS: Posterior vitreous detachment was the most common vitreomacular interface configuration (n = 154, 65%), followed by vitreomacular adhesion (n = 51, 22%) and release of vitreomacular adhesion (n = 32, 13%). The distribution of vitreomacular interface configurations among the treatment arms as well as baseline characteristics were balanced as shown in Tables 1 and 2.

• VISION OUTCOMES BY VITREOMACULAR INTERFACE CONFIGURATION: In the ranibizumab monotherapy arm, mean BCVA gains from baseline to the end of the loading phase at month 3 were +8.4 for posterior vitreous detachment, +4.7 for release of vitreomacular adhesion, and +6.6 for vitreomacular adhesion (P = .420). During PRN maintenance therapy from month 3 until month 12, mean letter changes were -5.0 for posterior vitreous detachment, -0.4 for release of vitreomacular adhesion, and +0.6 for vitreomacular adhesion (P = .070). In the ranibizumab plus verteporfin combination arm, mean letter gains at the end of the loading phase were +2.7 for posterior vitreous detachment, +6.5 for release of vitreomacular adhesion, and +9.3 for vitreomacular adhesion, showing superior outcomes for vitreomacular adhesion and release of vitreomacular adhesion with statistical significance at P = .042. This difference was maintained during PRN maintenance until month 12, with mean changes of -3.1letters for posterior vitreous detachment, +0.8 for release of vitreomacular adhesion, and +0.0 for vitreomacular adhesion (P = .212). Figure 2 shows BCVA results over time, comparing the vitreomacular interface groups in the monotherapy and combination therapy arms.

• IMPACT OF VITREOMACULAR INTERFACE CONFIGURA-TION ON MONOTHERAPY VS COMBINATION THERAPY: In patients with posterior vitreous detachment, mean letter gains after the loading phase were +8.4 with monotherapy and +2.7 with combination therapy, showing a highly significant advantage for monotherapy in patients with posterior vitreous detachment (P = .003). This statistical significance was maintained over the entire follow-up of 12 months. Mean changes during PRN maintenance from month 3 until month 12 were -5.0 with monotherapy and -3.1 with combination therapy, without significant difference (P = .296).

In patients with vitreomacular adhesion, combination therapy demonstrated superior visual outcomes during the early treatment phase; however, mean gains at month 3 were not statistically different at +6.6 letters in monotherapy and +9.3 in combination therapy, P = .406. Mean changes during PRN maintenance until month 12 were +0.6 letters with monotherapy and +0.0 with combination therapy, P = .836.

No significant differences were observed in patients with release of vitreomacular adhesion, with mean changes at month 3 of +4.7 letters in monotherapy and +6.5 with



FIGURE 2. Best-corrected visual acuity response in the vitreomacular interface groups. With ranibizumab monotherapy (Top), all vitreomacular interface groups show comparable results. However, with verteporfin plus ranibizumab combination therapy (Bottom), the subgroup with vitreomacular adhesion (squares) demonstrates superior benefits compared to patients with posterior vitreous detachment (filled squares). BCVA, best-corrected visual acuity.

combination therapy, P = .661. From month 3 to month 12, mean letter changes were -0.4 with monotherapy and +0.8 with combination therapy, P = .632. Figure 3 shows BCVA over time in monotherapy vs combination therapy in patients with posterior vitreous detachment, release of vitreomacular adhesion, and vitreomacular adhesion.

• RETREATMENT RATES BY VITREOMACULAR INTERFACE GROUPS: In the monotherapy arm, patients with posterior vitreous detachment received significantly fewer ranibizumab retreatments, with a mean number of retreatments after the loading phase at 4.9 in posterior vitreous detachment, 6.6 in release of vitreomacular adhesion, and 5.3 in vitreomacular adhesion, P = .018. No significant differences were observed in the combination therapy arm,



FIGURE 3. Monotherapy vs combination therapy in the vitreomacular interface groups: functional outcomes. In patients with posterior vitreous detachment (Top), the administration of PDT (squares) results in a loss of functional benefit compared to ranibizumab monotherapy (filled squares). Fewer differences are seen in the other vitreomacular interface groups, although patients with vitreomacular adhesion (Bottom) show an early benefit of PDT (squares) over ranibizumab monotherapy (filled squares). No significant differences between the two treatment arms are seen for patients with release of vitreomacular adhesion (Middle). BCVA, best-corrected visual acuity; PDT, photodynamic therapy.

where the mean number of ranibizumab retreatments was 4.7 in posterior vitreous detachment, 5.2 in release of vitreomacular adhesion, and 5.8 in vitreomacular adhesion, P = .101. The mean number of verteporfin PDT retreatments was 1.9 in posterior vitreous detachment, 1.5 in release of vitreomacular adhesion, and 2.1 in vitreomacular adhesion, P = .313.

• ANATOMIC RESPONSE BY VITREOMACULAR INTERFACE GROUPS: In the ranibizumab monotherapy arm, the mean changes in central retinal thickness from baseline to month 12 were  $-113 \ \mu m$  in posterior vitreous detachment,  $-89 \mu m$  in release of vitreomacular adhesion, and  $-122 \,\mu m$  in vitreomacular adhesion, without statistically significant difference, P = .725. In the ranibizumab plus verteporfin combination therapy arm, mean central retinal thickness changes at month 12 were  $-121 \ \mu m$  in posterior vitreous detachment, -113 µm in release of vitreomacular adhesion, and  $-113 \mu m$  in vitreomacular adhesion, without significant differences, P = .924. Patients with posterior vitreous detachment showed a trend for a quicker central retinal thickness response during the loading phase with combination therapy; however, this was not maintained over the 12 months of the study. Central retinal thickness responses over time in the vitreomacular interface groups are shown in Figure 4.

### DISCUSSION

THIS STUDY INVESTIGATED THE INFLUENCE OF THE VITREOmacular interface condition on the efficacy of ranibizumab monotherapy and ranibizumab plus verteporfin PDT combination therapy for neovascular AMD. Since the overall trial design was based exclusively on a PRN strategy, this setting provides an ideal opportunity to analyze vision results and retreatment frequencies. Whereas previous trials failed to detect a significant difference between combination and monotherapy, the stratification for vitreomacular interface configuration in our study allowed for identification of distinct response patterns. Posterior vitreous detachment, the most frequent vitreomacular interface condition in the typical AMD age group, resulted in a significant inferiority of the combination regimen that appeared as early as month 1 and persisted throughout the entire study year. In contrast, patients with vitreomacular adhesion demonstrated a diametrically opposite profile, with clear, early, and sustained benefit from verteporfin plus ranibizumab combination therapy. Our results, in line with previously published outcomes, may have significant implications on individual patient management in the era of personalized medicine. They may also impact treatment for the increasingly diagnosed variant of AMD-polypoidal choroidal vasculopathy, in



FIGURE 4. Monotherapy vs combination therapy by vitreomacular interface groups: anatomic outcomes. Apart from a more rapid reduction in central retinal thickness in the combination therapy arm (squares) in patients with posterior vitreous detachment (Top), no significant differences were observed between ranibizumab monotherapy and combination therapy with verteporfin in the other two vitreomacular interface configurations (Middle and Bottom). CRT, central retinal thickness.

which combination therapy with PDT is the standard management.

The vitreomacular interface configuration in AMD has attracted scientific interest only in recent years, likely owing to optimized visualization using continuous OCT imaging. Vitreous adhesions seem to be more common in patients with CNV, probably as a secondary consequence of inflammatory processes at the level of the vitreoretinal junction.<sup>31-34</sup> There is currently no evidence that vitreomacular adhesion per se might promote CNV development in patients with early AMD.<sup>35</sup> Published scientific reports on the influence of the vitreomacular interface configuration on CNV treatment are largely limited to retrospective studies in heterogeneous patient populations under "standard of care" treatment conditions, with the exception of 1 large-scale prospective study by our group.<sup>13,14,21</sup> In general, most studies conclude that patients with vitreomacular adhesion achieve poorer outcomes compared to patients without vitreomacular adhesion. On the other hand, we were recently able to show that patients with vitreomacular adhesion and release of vitreomacular adhesion could achieve excellent vision outcomes as long as treatment is performed in an aggressive and continuous fashion (i.e., monthly injections of an anti-VEGF agent).<sup>21</sup> By contrast, patients with posterior vitreous detachment were shown to achieve moderate outcomes regardless of the treatment scheme.

Considering both published scientific literature and the current study, there is now solid evidence that the presence of a posterior vitreous detachment leads to adequate outcomes regardless of the applied dosing strategy. Consistent with our previous report, this study demonstrated that patients with posterior vitreous detachment required significantly less retreatment after the loading phase in an investigator-driven PRN regimen using ranibizumab monotherapy. Despite the low number of retreatments, vision outcomes in the monotherapy arm were favorable and consistent in magnitude with other PRN studies and our previous publication. We can conclude from these findings that patients with posterior vitreous detachmentidentifiable by OCT at presentation-may be treated in a safe and effective manner using a personalized, discontinuous treatment approach.

Combination therapy with verteporfin in patients with posterior vitreous detachment, on the other hand, resulted in a reduction of potential vision gain already in the earliest phase of the study. This relative loss of vision is potentially attributable to the vaso-occlusive effect of PDT on the exposed choriocapillaris and subsequent damage to the neurosensory retina, particularly when using standard-(full-) fluence PDT.<sup>36</sup> Nevertheless, verteporfin treatment effectively suppresses CNV growth and leakage, as shown by the rapid and sustained effect on central retinal thickness in the PDT arm. The potential damaging effect of PDT becomes particularly visible in posterior vitreous detachment, which requires fewer retreatments.

Contrasting the well-defined population characterized by posterior vitreous detachment, patients with other vitreomacular interface configurations such as release of vitreomacular adhesion and stable vitreomacular adhesion show a much more heterogeneous outcome pattern, with variable response profiles by treatment regimen. In consideration of our previous results (demonstrating that these patients achieve unfavorable outcomes unless monthly injections are performed), it is confirmatory to see only moderate vision gains in this group under a PRN monotherapy regimen. Although the criteria for retreatment indication were less strict in the MONT BLANC study as compared to the "zero tolerance" regimen used currently, patients with vitreomacular adhesion and release of vitreomacular adhesion received significantly more injections than patients with posterior vitreous detachment. Despite the less specific response patterns in patients with vitreomacular adhesion and release of vitreomacular adhesion-which could also be attributed to sample size limitations—our results imply that this defined patient subgroup should preferentially not be switched to a discontinuous treatment regimen in clinical practice.

Moreover, patients with vitreomacular adhesion showed a durable beneficial effect of verteporfin combination therapy on functional outcomes as early as at month 2. Although functional differences in this rather small patient group should not be overinterpreted, we may speculate that patients with vitreomacular adhesion could benefit from primary combination therapy of ranibizumab and verteporfin.

We have previously theorized that pharmacokinetic mechanisms impacting distribution, metabolism, or clearance of anti-VEGF antibodies within the vitreous space may be responsible for the distinctive behavior of the various vitreomacular interface subtypes in terms of vision response and injection frequency.<sup>21</sup> Our current findings on the efficacy of PDT may alternatively indicate that eyes with vitreomacular adhesion may exhibit additional disease components, such as inflammation or mechanic stress, which are better amendable by PDT, a more intensive treatment targeting the neovascular structure directly. Clearly, our clinical observations can only generate hypotheses in this regard, and experimental studies should follow to add pathomechanistic insight.

This study has limitations in its employed imaging technology and sample size. Stratus OCT, the gold-standard technology at the time the MONT BLANC trial was performed, has less power to image the vitreous as compared to modern spectral-domain and swept-source OCT systems. The differentiation between complete vitreous attachment and complete posterior vitreous detachment is especially challenging and sometimes impossible on Stratus images. However, a high degree of diagnostic accuracy can be achieved if multiple consecutive examinations are used to categorize patients, as was done in this study.<sup>21</sup> In the AMD age group, where posterior vitreous detachment is reported to be 16–20 times more frequent than complete vitreous attachment, diagnostic errors with Stratus OCT as compared to spectral-domain OCT occur in a magnitude of only 2% of cases and are therefore negligible.<sup>35,37</sup>

Moreover, our ability to draw conclusions on the vitreomacular interface subgroups vitreomacular adhesion (n = 51) and release of vitreomacular adhesion (n = 32) are limited owing to small sample size. This limitation affects all studies on vitreous adhesion in neovascular AMD, as this particular vitreomacular interface configuration is generally rare in the respective patient population. It is important to note, however, that conclusions on patients with posterior vitreous detachment are supported by a highly adequate sample size in this vitreomacular interface category.

In conclusion, our study adds further evidence that the vitreomacular interface configuration significantly impacts vision response profiles in anti-VEGF treatment even if combined with verteporfin PDT for neovascular AMD. Patients with posterior vitreous detachment demonstrated adequate BCVA response using PRN ranibizumab monotherapy, while the application of combination PDT resulted in a significant loss of potential vision gain. In contrast, patients with vitreomacular adhesion and release of vitreomacular adhesion showed a trend toward more favorable outcomes in combination therapy using verteporfin plus ranibizumab. In clinical practice, the results of our trial may support an individual selection of the most adequate treatment approach and regimen, whereas future clinical trial designs may require stratifying patients by vitreomacular interface configuration.

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**Biosketch** 

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