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Vitreomacular Interface after Anti–Vascular Endothelial Growth Factor Injections in Neovascular Age-Related Macular Degeneration

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Purpose: To evaluate the incidence of posterior vitreous detachment (PVD) induced by intravitreal injections of anti–vascular endothelial growth factor (VEGF) agents in cases of neovascular age-related macular degeneration (AMD).

Design: Cohort study conducted at a single tertiary referral vitreoretinal practice.

Participants: A total of 396 eyes of 295 patients were diagnosed with neovascular AMD between 2009 and 2014. A total of 125 eyes of 112 patients met the inclusion criteria and were evaluated in this study.

Methods: This study included patients with neovascular AMD who presented vitreomacular adhesion (VMA) detected by spectral-domain optical coherence tomography (OCT) at baseline. Eyes with VMA were classified according to the diameter of vitreous attachment to the macular surface measured by OCT, with attachment of $\leq$1500 μm defined as focal and attachment of >1500 μm defined as broad. All patients received at least 3 monthly intravitreal injections of anti-VEGF agents. Follow-up visits were performed 1 month after each intravitreal injection and included OCT analysis to evaluate the incidence of PVD.

Main Outcome Measures: Posterior vitreous detachment induced by anti-VEGF injections.

Results: The mean follow-up period was 21.3 months (range, 3–59 months). The mean number of intravitreal injections was 8.3 (range, 3–29 injections). Intravitreal drugs used in the study were ranibizumab (51.5%), bevacizumab (33.5%), and aflibercept (15.0%). Seven eyes (5.6%) developed PVD after intravitreal drug injection (3 eyes after the first intravitreal injection: bevacizumab in 1 and ranibizumab in 2; 2 eyes after the second injection: ranibizumab in 1 and bevacizumab in 1; 1 eye after the fourth injection: ranibizumab; and 1 eye after the sixth injection: aflibercept). A total of 118 eyes remained with persistent VMA. All 7 eyes that developed PVD were classified as having focal VMA, with the diameter of vitreous attachment ranging from 210 to 1146 μm (mean, 600 μm).

Conclusions: Intravitreal injections of commonly used anti-VEGF intravitreal drugs rarely induce PVD in patients with neovascular AMD. Eyes with focal VMA have a greater chance to develop PVD than eyes with a broad area of VMA. *Ophthalmology 2015;■:1–4 © 2015 by the American Academy of Ophthalmology.*

Vitreomacular adhesion (VMA) seems to play a role in the development of macular pathologies, including age-related macular degeneration (AMD).[1] Previous studies have considered persistent VMA as a possible risk factor for the development of neovascular AMD, whereas posterior vitreous detachment (PVD) seems to protect against this form of the disease.[1–4] A recent subanalysis of a randomized, double-masked, multicenter study has also shown that the configuration of the vitreomacular interface (VMI) seems to have an important effect on visual outcomes and need for re-treatment in cases of neovascular AMD. In patients with PVD, a lower treatment frequency may be feasible, whereas patients with VMA may benefit from intensive re-treatment.[5]

It is still not established whether intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors itself could induce PVD. Only 1 previous study evaluated its occurrence after intravitreal drug injection for different macular pathologies and showed that this procedure may favor the occurrence of PVD.[6] Therefore, PVD possibly induced by intravitreal injection could itself benefit the response to treatment. The purpose of this study is to evaluate the incidence of PVD induced by intravitreal injections of anti-VEGF agents in cases of neovascular AMD.

Methods

This is a prospective study designed to evaluate the incidence of PVD after intravitreal injections of currently used anti-VEGF drugs for neovascular AMD. All subjects were informed about the nature of the study and signed a written informed consent in accordance with the tenets of the Declaration of Helsinki. The ethics committees of both the Federal University of Minas Gerais and the Institute of Vision in Belo Horizonte, Brazil, approved the study. From March 2009 to December 2014, all patients with newly

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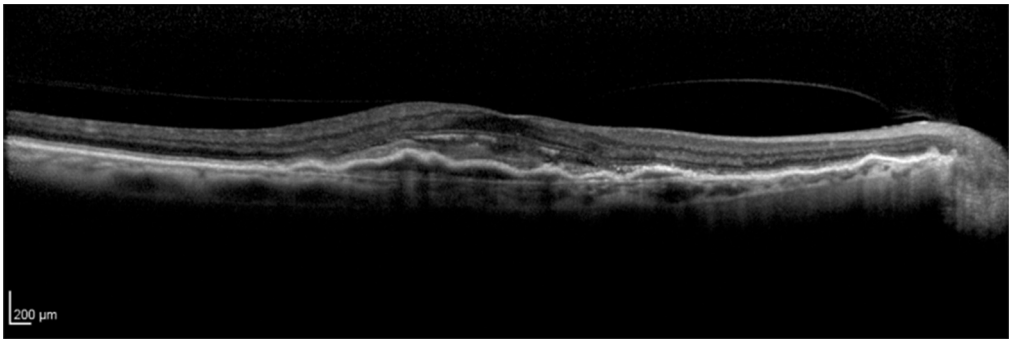

Figure 1. Example of an optical coherence tomography scan showing the presence of vitreomacular adhesion.

diagnosed neovascular AMD at the Institute of Vision were enrolled in this prospective study. At baseline, all patients underwent a complete ophthalmological examination, including biomicroscopy, retinography, fluorescein angiography, and optical coherence tomography (OCT). When indicated, indocyanine green angiography was performed for better evaluation of neovascular AMD subtypes. Spectral-domain OCT (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) was used to evaluate the VMI. Only eyes with VMA present (Fig 1) were included in the study. Vitreomacular adhesion was defined as any adhesion of the posterior hyaloid involving the macular region (area: 8.8×5.9 mm, 30°×20°, 25-scan pattern). Patients with VMA were classified according to the diameter of vitreous attachment to the macular surface measured by OCT, with attachment of ≤1500 µm defined as focal and attachment of >1500 µm as broad. When there was no posterior hyaloid visible or when it was detected but not attached to the scanned area, we considered the vitreous to be detached. Inclusion criteria were (1) age >50 years; (2) diagnosis of neovascular AMD; (3) presence of VMA at baseline detected by OCT; (4) indication of intravitreal injection of VEGF inhibitors; and (5) follow-up of at least 3 months. Intravitreal drugs used in this study included bevacizumab (Avastin; Genentech, South San Francisco, CA), ranibizumab (Lucentis; Genentech), and aflibercept (Eylea; Regeneron Pharmaceuticals Inc., Tarrytown, NY). The injected volume of VEGF inhibitors was 0.05 ml for ranibizumab and aflibercept and 0.1 ml for bevacizumab. Exclusion criteria were (1) previous vitrectomy; (2) complicated cataract surgery; (3) concomitant inflammatory ocular conditions; (4) eyes with other conditions that are known to affect the VMI, such as retinal vascular disease, pathologic myopia, and diabetic retinopathy; (5) detectable PVD on OCT (Fig 2) or slit-lamp examination; and (6) previous intravitreal injections. All intravitreal anti-VEGF injections were performed in the operating room using an aseptic technique, including the prophylactic use of topical iodopovidone 5% before the procedures. All patients were subjected to a treatment protocol that included a loading dose with 3 intravitreal injections of anti-VEGF agents at 1-month intervals. After the third dose, patients followed a pro re nata regimen. Retreatment criteria were (1) persistence or increase of intraretinal or subretinal fluid; (2) increase of retinal pigment epithelium detachment; (3) worsening of at least 1 line of visual acuity; and (4) new subretinal hemorrhage. Follow-up visits, including OCT, were schedule to be performed 1 month after each intravitreal injection. Optical coherence tomography was performed and its data were analyzed separately by 3 retinal specialists (C.E.V., T.M.K., F.B.P.). Each retinal physician was blinded to the classifications determined by the others. If there was any disagreement, they evaluated the data simultaneously and came to a consensus. All intravitreal injections were performed by a single retinal specialist (M.B.N.).

Results

A total of 396 eyes of 295 patients were diagnosed with neovascular AMD. From this total, 166 eyes (41.9%) presented with VMA. A total of 125 eyes of 112 patients met the inclusion criteria and were evaluated in this study. The mean age was 70.6 years (range, 52−84 years), and 62 patients (55.4%) were female. A total of 68 eyes (54.4%) were phakic, and 57 eyes (45.6%) were pseudophakic. The mean follow-up period was 21.3 months (range, 3−59 months). The mean number of intravitreal injections was 8.3 (range, 3−29 injections). Patients who developed PVD required a mean of 7.9 injections, and patients with persistent VMA required a mean of 8.3 injections. Intravitreal drugs used in the study were ranibizumab (51.5%), bevacizumab (33.5%), and aflibercept (15.0%). Seven eyes (5.6%) developed PVD after intravitreal drug injection (3 eyes after the first intravitreal

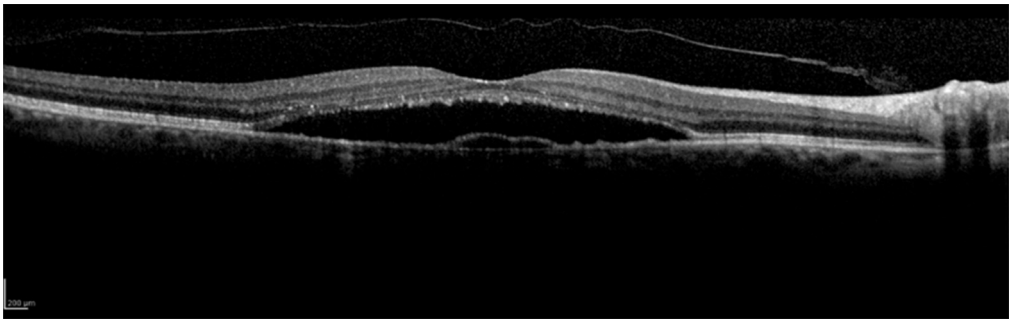

Figure 2. Example of optical coherence tomography scan showing posterior vitreous detachment.