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Original Article

Prevalence of Polypoidal Choroidal Vasculopathy in Eyes with Neovascular Age-Related Macular Degeneration Resistant to Intravitreal Anti-VEGF Treatment

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Abstract

Objectives: To determine the prevalence of polypoidal choroidal vasculopathy (PCV) in intravitreal (IV) anti-vascular endothelial growth factor (anti-VEGF)-resistant neovascular age-related macular degeneration (nvAMD) cases.

Materials and Methods: Eyes that were diagnosed as having active and treatment-naive nvAMD in the Ege University Ophthalmology Department, Retina Unit in 2011-2018, were non-responsive to IV anti-VEGF treatment, and for which indocyanine angiography (ICGA) could be obtained were included in the study. Active nvAMD was defined as the presence of fresh hemorrhage on clinical examination or findings of subretinal, intraretinal, or sub-retinal pigment epithelial fluid on spectral domain optical coherence tomography and accompanying fluorescein dye leakage in fluorescein angiography. Eyes that had activation findings despite at least 6 consecutive intravitreal anti-VEGF injections were defined as non-responders and underwent ICGA to assess for PCV. The diagnosis of PCV was based on the Everest II study criterion.

Results: A total of 97 eyes of 88 patients were included in the study. Of 88 patients, 44 (50%) were female, 44 (50%) were male, and the mean age was 75.9±8.3 years (range: 59-93). The mean number of anti-VEGF injections until the time of ICGA was 7.3±2.2 (range: 6-15). PCV was detected in 62 eyes (63.9%) on ICGA.

Conclusion: The prevalence of PCV is quite high among eyes with IV anti-VEGF treatment-resistant nvAMD in Turkey (63.9%). ICGA evaluation for PCV should be conducted for all nvAMD cases that are non-responsive to IV anti-VEGF treatment, both to shed light on the reason for resistance and to modify treatment as necessary.

Keywords: Anti-VEGF, polypoidal choroidal vasculopathy, age-related macular degeneration

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Introduction

Intravitreal (IV) injection of anti-vascular endothelial growth factor (anti-VEGF) agents is currently regarded as the standard treatment method for active neovascular age-related macular degeneration (nvAMD). In large-scale prospective, multicenter, controlled phase III clinical trials, most eyes were reported to respond well to anti-VEGF treatments, with improved or preserved visual acuity and anatomical improvements in retinal hemorrhage and/or exudative changes.[1,2] However, despite these positive results, it is also known that a small proportion of eyes do not respond adequately to anti-VEGF drugs and show persistence and/or clinical deterioration.

The possible existence of nvAMD subtypes is considered one of the main reasons for poor response or resistance to anti-VEGF therapy.[3,4] Polypoidal choroidal vasculopathy (PCV), believed to be one of these subtypes, has a recurrent course characterized by polypoidal vascular dilations and/or abnormal branching vascular networks originating from the inner choroidal vessels that are frequently associated with serous and hemorrhagic retinal pigment epithelium (RPE) detachments.[4,5] Indocyanine green angiography (ICGA) examination is considered the gold standard to diagnose PCV and demonstrate the presence of polyps.[6] Studies on the prevalence of PCV have indicated a higher prevalence in the yellow race than in the white race, but also demonstrated considerably variation in rates among different populations and races.[7,8,9,10,11,12,13] Few studies have investigated the frequency of PCV among eyes that respond poorly to anti-VEGF therapy.[3,14,15,16,17]

Therefore, we conducted this clinical study in our center to determine the prevalence of PCV in eyes with nvAMD exhibiting inadequate response to IV anti-VEGF therapy.

Materials and Methods

This prospective cross-sectional clinical study included 97 eyes of 88 patients who were diagnosed with treatment-naive, active nvAMD in the Retina Unit of the Ege University Ophthalmology Clinic between 2011 and 2018, responded poorly to treatment with at least 6 consecutive IV anti-VEGF injections at intervals of 4-6 weeks, and underwent ICGA imaging. Eyes previously treated for nvAMBD, eyes that received fewer than 6 injections, eyes for which treatments could not be performed consecutively and regularly, and patients for whom indocyanine dye could not be obtained or who had a contraindication for ICGA were excluded from the study.

Informed consent forms were obtained from all patients and approval was obtained from the Ege University Clinical Research Ethics Committee (decision no: 12-2/47, 2013) and the Turkish Medicines and Medical Devices Agency (transaction no: 1135321/06.03.2013). The study was carried out in adherence to the tenets of the Declaration of Helsinki.

Eyes with fresh hemorrhage on clinical examination or subretinal (SR), intraretinal (IR), or sub-RPE fluid on spectral domain optical coherence tomography (SD-OCT) and associated leakage on fluorescein angiography (FA) were regarded as having active nvAMD. These eyes were treated with injections of ranibizumab (RBZ) (Lucentis; 0.5 mg/0.05 mL, Genentech Inc., San Francisco, CA, USA) or aflibercept (A) (Eylea; 2 mg/0.05 mL, Bayer/Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA) administered under fully sterile operating room conditions. At 4-6 weeks after IV anti-VEGF treatments, follow-up examinations were performed and best corrected visual acuity (BCVA) measurements, biomicroscopic fundus examination, and SD-OCT findings were evaluated. Eyes with persistent signs of activation in follow-up examinations at 4-6 weeks after the first three consecutive IV anti-VEGF injections continued treatment at the same intervals. For those without signs of activation, treatment intervals were extended by adding 2 weeks to the previous interval at each follow-up examination as per the "treat and extend" protocol.

Eyes with persistent signs of activation in the follow-up examination 1 month after the last treatment despite receiving at least 6 consecutive doses were accepted as nonresponders and ICGA was performed (Heilderberg Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany) in patients for whom the dye could be obtained. The EVEREST II criteria were used for the diagnosis of PCV.[14]

Results

Of the 88 patients included in the study, 44 (50%) were male and 44 (50%) were female, 9 (9.1%) had bilateral disease, and the mean age was 75.9±8.3 (range: 59-93) years. A total of 97 eyes were included. The mean number of injections administered was 7.3±2.2 (range: 6-15) and the mean follow-up period was 31.6±4 months (range: 8-90). The mean baseline BCVA was 0.63±0.46 logMAR (range: 0-1.8) and the mean cross-sectional BCVA at the time of ICGA was 0.62±0.14 logMAR (range: 0-1.8).

Anti-VEGF therapy consisted of RBZ in 89 eyes (91.7%), and 6 (6.18%) eyes were switched to A after receiving a mean of 8 (range: 5-11) doses of RBZ.

PCV was detected by ICGA in 62 (63.9%) of the eyes that did not respond to at least 6 (mean 7.3±2.2) consecutive anti-VEGF treatments. Figure 1 shows the fundus and OCT images from an eye with progressive exudative findings despite 9 IV anti-VEGF injections (Figure 1a-d). Figure 2 shows FA images obtained after the ninth injection (Figure 2a,b) and polyps on ICGA (Figure 2c,d) in the same eye.

Discussion

In this prospective, cross-sectional clinical study, we evaluated the frequency of PCV in 95 nonresponder eyes with persistent signs of activation on clinical examination and SD-OCT despite receiving at least 6 consecutive IV anti-VEGF injections, and determined it to be 63.9%.

Although IV anti-VEGF therapy is currently accepted as the standard treatment for nvAMD, it is known that signs of activation persist and even worsen despite treatment in a small proportion of eyes. In some of these eyes, which are called

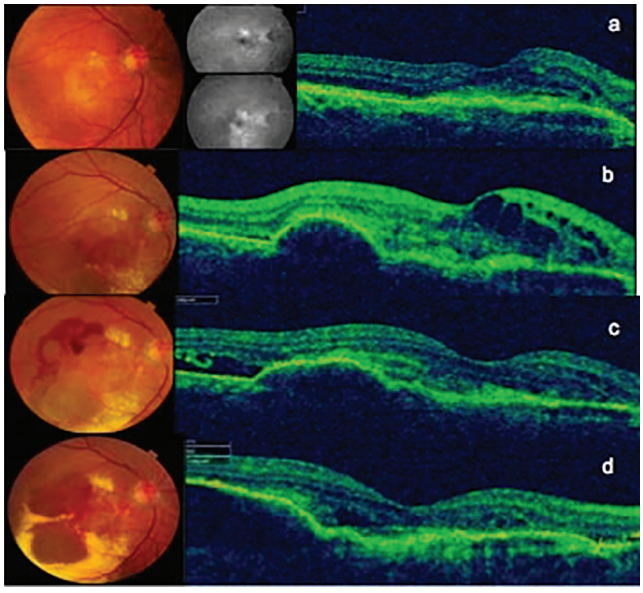

Figure 1. Color fundus photographs and spectral domain optical coherence tomography images of a patient who received intravitreal ranibizumab injections in the right eye for neovascular age-related macular degeneration: a) At first examination, b) After 3 injections, c) After 6 injections, and d) After 9 injections

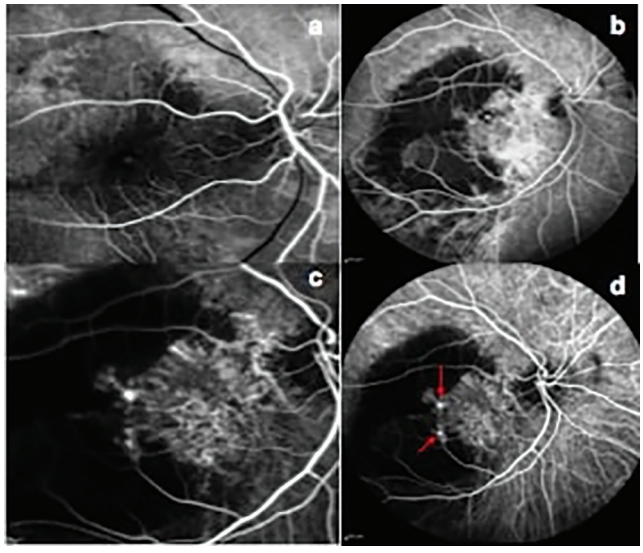

Figure 2. Angiographic images from the patient in Figure 1, after 9 injections: a) Early and b) late stage fluorescein angiography images; c) Early and d) late stage indocyanine green angiography images showing two polyps (red arrows)

nonresponders or resistant to treatment, the cause is believed to be AMD subtypes or diseases that mimic it, such as underlying PCV, retinal angiomatous proliferation, chronic central serous chorioretinopathy (CSCR), neovascularization secondary to CSCR, drusenoid pigment epithelial detachment, and adult vitelliform macular dystrophy.[17]

In the literature, the reported prevalence of PCV has differed considerably by country, ethnic group, and race. Rates up to 54.7% have been reported for the yellow race and Asian populations,[13] whereas frequencies of 4-9.8% are reported in Whites.[7,8,9,10] The frequency of PCV was found to be 8.2% in a study conducted in Greece among patients previously diagnosed with exudative AMD, while other studies reported rates of 9.8% in Italy, 24% in Korea, and 49.7% in India.[9,10,11,12] In our opinion, one of the main reasons for the difference in reported prevalence rates is the fact that ICGA, which is the gold standard for PCV diagnosis, is not routinely performed in many countries or clinics.

Although it is predicted that PCV may be much more frequent among eyes that do not respond to treatment, few studies have been conducted on this subject. Among these studies, all of which were retrospective, Kokame et al.[15] reported the prevalence of PCV as 50% in patients with nvAMD among nonresponders to IV anti-VEGF therapy and 30.2% among responders. In the same study, it was emphasized that the prevalence of PCV among treatment-resistant cases was 56.2% in Asian patients and 43.2% in the white race, while among treatment-sensitive cases these rates were 37.1% and 16.0%, respectively. In a study conducted in white patients in Switzerland, Hatz and Prünte[16] found the frequency of PCV to be 21.5% in patients resistant to at least 8 doses of IV RBZ and 3.8% in eyes that responded to treatment. Ozkaya et al.[17] reported the frequency of PCV to be 56.1% in their retrospective study investigating the role of ICGA in the differential diagnosis of eyes with nvAMD and poor response to IV RBZ.

Our study was conducted in Turkish patients presenting to our clinic, and the frequency of PCV was 63.9% in eyes that did not respond to at least 6 doses of IV anti-VEGF therapy. To the best of our knowledge, this is the first prospective study in the literature to investigate the frequency of PCV in Turkish patients with nvAMD who did not respond to IV anti-VEGF therapy. Our study results demonstrate that the frequency of PCV is quite high in this group. Compared to other studies in the literature, our rate appears to be closer to PCV prevalence rates reported for the Asian population.[12,13,15]

Considering that nearly all patients in our study received RBZ for the first 6 doses of anti-VEGF therapy and the injections were administered consecutively with regular follow-up, we believe that our study includes a very homogeneous group and this increases the reliability of our results. Because of the difficulties acquiring indocyanine dye in Turkey, ICGA was not among the routine diagnostic methods for newly diagnosed cases up to a year or two ago, and we believe that performing ICGA at the time of initial diagnosis and detecting the presence of PCV at the start may be important in terms of implementing different modifications to treatment and follow-up protocols.

Conclusion

Given the high frequency of PCV among the eyes that did not respond to IV anti-VEGF drug therapy, we believe that ICGA assessment for PCV in resistant eyes will both improve our understanding of the causes of treatment nonresponse and

provide guidance regarding the addition of different treatment alternatives to the treatment protocol.

Ethics

Ethics Committee Approval: Informed consent forms were obtained from all patients and approval was obtained from the Ege University Clinical Research Ethics Committee (decision no: 12-2/47, 2013) and the Turkish Medicines and Medical Devices Agency (transaction no: 1135321/06.03.2013). The study was carried out in adherence to the tenets of the Declaration of Helsinki.

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Authorship Contributions

Surgical and Medical Practices: J.M., Concept: J.M., Design: J.M., Data Collection or Processing: M.E.B., Analysis or Interpretation: J.M., M.E.B., Literature Search: M.E.B., Writing: M.E.B.

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