

Original Research Article

Effect of pseudoexfoliation on anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration

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Abstract

Purpose: To evaluate short-term outcomes of anti-vascular endothelial growth factor (anti-VEGF) treatment in patients with neovascular age-related macular degeneration (nAMD), with and without Pseudoexfoliation syndrome (PEX).

Methods: This retrospective study was carried out at Istanbul Bagcilar Training and Research Hospital, Istanbul, Turkey. Demographic and clinical examination data were collected from charts of patients treated between May 2014 and May 2019, and the cohort comprised 44 eyes from 43 patients. PEX group had 22 eyes from 17 patients diagnosed with both PEX and nAMD, while control group comprised 22 eyes from 21 patients diagnosed with nAMD only. Both groups were treatment-naïve patients who visited the clinic for the first time and all patients received at least three-monthly intravitreal injections of 1.25 mg/0.05 mL bevacizumab, 0.5 mg/0.1 mL ranibizumab, or 2 mg/0.05 mL aflibercept. The treatment response was evaluated at the 3-month follow-up using optical coherence tomography (OCT) and best corrected visual acuity (BCVA).

Results: Results show that BCVA was significantly improved from baseline in PEX group ($p = 0.002$) and control group ($p = 0.005$). Systemic hypertension and retinal pigment epithelium detachment were more common in PEX group than in control group ($p = 0.031$ and $p = 0.035$, respectively). Lesion thickness on OCT decreased from $594.31 \pm 218.04 \mu\text{m}$ to $427.63 \pm 118.43 \mu\text{m}$ in PEX group ($p < 0.001$) and from $570.72 \pm 202.58 \mu\text{m}$ to $417.90 \pm 153.07 \mu\text{m}$ in control group ($p = 0.003$). Although the central macular thickness decreased in PEX group, the difference was not significant ($p = 0.064$).

Conclusion: Anti-VEGF treatment is an effective option in nAMD patients with PEX. Prospective, randomized studies may clarify the interactions between PEX, nAMD and anti-VEGF treatment.

Keywords: VEGF, Anti-VEGF, Macular degeneration, Pseudoexfoliation

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INTRODUCTION

Neovascular age-related macular degeneration (nAMD) is a major cause of irreversible vision loss in the elderly and it is characterized by growth of abnormal blood vessels from the

choroid, a process known as choroidal neovascularization [1]. These vessels then disrupt retinal pigment epithelium, leading to fluid leakage, bleeding and finally scarring. Patients with nAMD typically report symptoms such as central visual distortion (metamorphopsia),

decreased best corrected visual acuity (BCVA) and the presence of a central scotoma [2].

Pseudoexfoliation syndrome (PEX) is an age-related systemic disorder in which ocular structures and vascular endothelium are disturbed, secondary to accumulation of abnormal extracellular fibrillary material [3]. This material accumulates in ocular structures, such as on the lens capsule, zonules, iris, trabecular meshwork and ciliary body, and contributes to both structural and vascular dysfunction. This syndrome is usually associated with glaucoma, high intraocular pressure and impaired ocular blood flow [4]. The presence of PEX increases complication rates in intraocular surgeries and interferes with the progression or treatment response in several ocular conditions, including retinal vein occlusion and macular edema [5,6].

Both conditions (PEX and nAMD) are severe conditions of the aging eye with several treatment challenges and the efficacy of standard treatments for patients with coexisting PEX and nAMD is unknown [7]. Currently, nAMD treatment is based on intravitreal delivery of anti-vascular endothelial growth factor (anti-VEGF) agents, such as bevacizumab, ranibizumab, and aflibercept [8], which helps to decrease neovascular leakage and halt disease progression. While these drugs act in similar ways, they show differences in molecular composition, half-life and cost, potentially resulting in unpredictable responses among patients [9]. Since PEX does not have a known specific, disease-modifying treatment, current management protocols are mainly directed at reducing its various complications, especially glaucoma, which constitutes a significant cause of morbidity in affected patients [4].

Previous studies have consistently demonstrated increased concentrations of vascular endothelial growth factor (VEGF) within both the aqueous humor and serum of PEX patients [10,11]. Studies are needed to determine the therapeutic efficacy of anti-VEGF drugs in patients with both PEX and nAMD. Thus, this investigation compared short-term clinical findings following intravitreal anti-VEGF therapy in patients with only nAMD and those with both PEX and nAMD by evaluating quantitative optical coherence tomography (OCT) parameters and changes in visual acuity.

METHODS

This retrospective case-control study was conducted at Saglik Bilimleri University, Istanbul Bagcilar Training and Research Hospital, a

tertiary referral center in Istanbul, Turkey. Ethical approval was granted by the Ethics Committee of Bagcilar Training and Research Hospital (protocol number: 2019.03.3.02.031). Informed consent was signed by all participants. The principles detailed in the Declaration of Helsinki in this study were strictly adhered to and files of patients who were followed up in the retina clinic of the Ophthalmology Department between May 2014 and May 2019 were reviewed. The retina clinic is a subspecialty unit within the Ophthalmology Department, where patients with posterior segment diseases, such as nAMD, are diagnosed and treated.

Patient selection and data collection

The patient cohort included two groups; the first group comprised 21 patients (22 eyes) with only nAMD (control group) while the second group was composed of 17 patients (22 eyes) with both PEX and nAMD (PEX group). Demographic and clinical examination data were retrieved from the patients' charts. Both groups were composed of treatment-naïve patients who visited the clinic for the first time. Choroidal neovascularization arises from causes other than age-related macular degeneration; hence, patients with choroidal neovascularization not attributable to nAMD were excluded from this investigation. Other exclusion criteria for both groups were the previous diagnosis of diabetes mellitus, hereditary retinal dystrophy and retinal vascular occlusion. Since the timing and nature of previous intraocular surgeries could not be determined accurately, patients who were found to have undergone intraocular surgery at their first examination were not included in this study. Characteristic gray-white pseudoexfoliation material on the lens surface and iris borders observed by slit-lamp examination was used for the diagnosis of pseudoexfoliation in patients in PEX group. In the literature, when the efficacy of one anti-VEGF molecule was considered inadequate for treating nAMD, variations in efficacy were noted upon transitioning to an alternative [12]. Consequently, the eyes of patients who altered their therapy were also excluded from this investigation.

All patients received at least three monthly injections of intravitreal anti-VEGF drugs comprising 1.25 mg/0.05 mL bevacizumab (Altuzan, F. Hoffmann-La Roche Ltd., Basel, Switzerland), 0.5 mg/0.1 mL ranibizumab (Lucentis Genentech Inc., San Francisco, CA, USA, and Novartis Pharma AG, Basel, Switzerland), and 2 mg/0.05 mL aflibercept (Eylea Regeneron Pharmaceuticals Inc., Bayer, Basel, Switzerland) [13]. The baseline and follow-up control examination findings of the third

dose of anti-VEGF injection were evaluated. The demographic and complete ophthalmological examination data, including best-corrected visual acuity (BCVA) and Goldmann applanation tonometer intraocular pressure (IOP) measurements of the patients, were collected from the files of patients. Also, Snellen chart BCVA measurements were converted into LogMAR values for statistical purposes. In addition, the usage of glaucoma drugs at baseline and last follow-up visit was checked from medical records. Furthermore, baseline and follow-up retinal thicknesses were measured using OCT (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) and analyzed to compare treatment responses [14]. The retinal thickness measurements were obtained from the internal limiting membrane of the retina to the choroid at the level of choroidal neovascularization and central macula. Patients with pigment epithelium detachment (PED) were identified from their optical coherence tomography. The fundus angiographies (Visucam 500, Carl ZeissMeditec AG, Goeschwitzer Strasse 51-52, Germany) taken at baseline were checked for the presence of retinal hemorrhage.

Statistical analysis

Data were analyzed with the PSPP program (PSPP, GNU Operating System, <https://www.gnu.org/>). Qualitative data were analyzed by Chi-square test and Fisher's exact test. In contrast, quantitative data were analyzed with Mann-Whitney U test, Wilcoxon signed-rank test, or McNemar method, as appropriate. Results of quantitative values are shown as mean $\pm$ standard deviation (mean $\pm$ SD (range)). *P*-values less than 0.05 were determined to be statistically significant.

RESULTS

Baseline characteristics of patients

This study evaluated files of 882 patients who had been followed for nAMD. Thirty-five patients had coexisting PEX and nAMD. Of those 35

patients, 18 did not meet the inclusion criteria because of reasons including insufficient follow-up, diabetes mellitus, and intraocular surgery. Thus, 22 eyes from 17 patients were included in PEX group of this study. Control group comprised 22 eyes from 21 consecutive eligible nAMD patients without PEX.

Baseline characteristics of the patients are shown in Table 1. Mean age of PEX group was 74.5 ± 7.9 years, which was significantly higher than control group (68.8 ± 8.1 years; $p = 0.016$). Nine eyes (40.9 %) from women and 13 eyes (59.1 %) from men were treated in PEX group. In control group, 7 eyes (31.8 %) of the patients were from women and 68.2 % of the eyes were from men. There was no statistical difference between the sex distribution of both groups ($p = 0.53$). Furthermore, in PEX group, two eyes (9.1%) were treated with bevacizumab, five eyes (22.7 %) with ranibizumab and 15 eyes (68.2 %) with aflibercept. On the other hand, two eyes (9.1 %) were treated with bevacizumab, six eyes (27.3 %) with ranibizumab and 14 eyes (63.6 %) with aflibercept in control group. Drug distribution between groups was not different from each other ($p = 1.0$).

Complete ophthalmological examination data

Mean BCVA improved significantly in both groups. In PEX group, BCVA increased from 1.27 ± 0.89 to 0.95 ± 0.63 LogMAR ($p = 0.002$) while the increase in BCVA was from 0.74 ± 0.40 to 0.54 ± 0.41 LogMAR ($p = 0.005$) in control group. PEX group had a significantly lower initial BCVA ($p = 0.029$) and this difference remained significant at the last follow-up visit ($p = 0.034$). Tables 2 and 3 show the mean OCT values before and after treatment. The OCT thicknesses over the lesion were decreased significantly in both the PEX and control groups ($p < 0.001$ and $p = 0.003$, respectively) while the central macular thickness was decreased in control group ($p = 0.007$), but there was no statistically significant improvement in the central macular thickness in the group with PEX ($p = 0.064$).

Table 1: Demographic and baseline examination findings of the groups

Parameter	PEX group	Control group	<i>P</i> -value
Age (years)	74.5 ± 7.9 (57–85)	68.8 ± 8.1 (58–86)	$p1=0.016$
Intraocular pressure (mmHg)	17.7 ± 3.4 (12–25)	16.5 ± 1.9 (14–21)	$p1=0.2$
Systemic hypertension (n)	8	2	$p2=0.031$
PED (n)	15	8	$p3=0.035$
IRH or SRH (n)	1	6	$p2=0.095$

Values are represented as mean $\pm$ SD (range). PEX = Pseudoexfoliation, PED = pigment epithelium detachment, IRH = intraretinal hemorrhage and SRH = subretinal hemorrhage. P1 refers to Mann–Whitney U test results, p2 refers to Fisher's exact test, and p3 refers to Chi-square test results

Table 2: Mean optical coherence tomography values of the groups before and after treatment

Parameter	PEX group	Control group	P ₁ -value
Baseline lesion OCT thickness (μm)	594.31±218.09 (279–1232)	570.72±202.58 (229–990)	0.89
Last visit lesion OCT thickness (μm)	427.63±181.43 (252–1076)	417.90±153.07 (200–762)	0.83
P ₂ -value	<0.001	0.003	

Values are represented as mean ± SD (range). PEX = Pseudoexfoliation and OCT = optical coherence tomography. *P*₁ denotes Mann–Whitney U test results at baseline and last follow-up visits of the PEX and control groups; *p*₂ denotes Wilcoxon test results for the comparison of baseline and last follow-up examinations of OCT thickness in the PEX and control groups.

Table 3: Central macular OCT measurement values of the groups before and after treatment

Parameter	PEX group	Control group	P ₁ -value
Baseline lesion OCT thickness (μm)	328.0±155.76 (162–711)	385.13±165.51 (179–925)	0.17
Last visit lesion OCT thickness (μm)	258.90±105.65 (154–555)	278.54±135.42 (161–705)	0.97
P ₂ -value	0.064	0.007	

Values are represented as mean ± SD (range). PEX = Pseudoexfoliation and OCT = optical coherence tomography. *P*₁ denotes Mann–Whitney U test results at baseline and last follow-up visits of the PEX and control groups; *p*₂ denotes Wilcoxon test results for the comparison of baseline and last follow-up examinations of central macular OCT thickness

DISCUSSION

This study evaluated the short-term effects of intravitreal anti-VEGF treatment in patients with coexisting nAMD and PEX. Anti-VEGF treatments improved both BCVA and OCT measurements over the lesion in nAMD regardless of PEX status (*p* = 0.002 and *p* < 0.001, respectively). However, although the central macular thickness decreased following treatment in control group, there was no statistically significant decrease from the baseline in PEX group following treatment (*p* = 0.064).

Pseudoexfoliation syndrome causes alterations in most segments of the eye, including the retinal and choroidal vasculature [6,15]. Vascular endothelial growth factor (VEGF) is a critical factor for the development of nAMD and anti-VEGF drugs such as bevacizumab, ranibizumab and aflibercept are useful in the treatment of this disease [13]. Previous studies have revealed increased VEGF concentrations in the aqueous humor and serum of PEX patients [10,11].

Several biochemical and structural endpoints, such as VEGF levels and OCT findings, have been evaluated in PEX patients to determine a potential therapeutic target. Hu and colleagues found increased serum and aqueous humor VEGF concentrations in pseudoexfoliation glaucoma compared with cataract patients [10]. Similarly, Borazan and colleagues found increased mean aqueous humor and plasma VEGF concentrations in PEX patients compared to controls [11]. In addition to biochemical findings, Çınar and colleagues demonstrated structural vascular alterations, including a substantial reduction in superficial retinal blood

flow and vessel density in eyes with PEX compared to healthy eyes [6]. They concluded that the enlargement of the foveal avascular zone in both superficial and deep retinal layers reinforces the existence of PEX-related vascular damage [6]. In a recent study, choroidal vessel density was investigated with OCT angiography and found to be lower in patients with PEX. The present study showed beneficial effects of anti-VEGF drugs, as shown by thinner OCT measurements over the lesion (*p* < 0.001) in PEX patients, although central macular thickness did not significantly improve (*p* = 0.064).

Systemic hypertension and vascular diseases are seen in PEX due to the accumulation of PEX material in the endothelium. Although some studies have demonstrated a higher rate of arterial hypertension in patients with PEX, a clear association has not been confirmed between PEX and systemic hypertension [15,16]. Borazan and colleagues showed increased aqueous humor and plasma VEGF concentrations in PEX patients, but they found no difference in the incidence of systemic hypertension in PEX patients compared to control group [11]. The current study found more hypertensive patients in PEX group compared to control group, and this difference was statistically significant (*p* = 0.031). The presence of PED or hemorrhage in nAMD patients requires follow-up [17]. In nAMD patients, the incidence of PED was up to 80 % [18], while some reports relate hypertension and retinal hemorrhage in nAMD [19]. In this study, the rate of PED in PEX group (68.2 %) was higher than control group (31.8 %; *p* = 0.035). Also, an increased but statistically insignificant rate of hemorrhagic lesions was observed in control group compared to PEX group (*p* = 0.095).

Limitations of this study

This study has some limitations that should be acknowledged. First, its retrospective design is naturally prone to selection bias and limits the capacity to show causality. Second, the short-term follow-up duration may not fully capture the long-term consequences of anti-VEGF treatment in individuals with coexisting PEX and nAMD.

CONCLUSION

This short-term analysis shows the benefit of the current dosage and treatment protocol of anti-VEGF drugs in patients with both PEX and nAMD. Prospective, randomized studies may clarify the interactions between PEX, nAMD and anti-VEGF treatment in the future.

DECLARATIONS

Acknowledgement/Funding

None.

Ethical approval

Ethical approval was granted by the Ethics Committee of Bagcilar Training and Research Hospital, Istanbul (approval no. 2019.03.3.02.031).

Use of Artificial intelligence/Large language models

We also declare that we did not use Generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Kursat Atalay reviewed the literature, collected and analyzed

the data, and drafted and critically revised the manuscript. Havva Kaldirim collected the data and critically revised the manuscript. Fatma Savur critically revised the manuscript. Mustafa Gurkan Erdogan critically revised the manuscript.

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