Intraocular Pressure Changes in Eyes Treated with Intravitreal Injections of Anti-Vascular Endothelial Growth Factor for Age Related Macular Degeneration: The Results of Real Worlds

Yaşa Bağlı Makula Dejenerasyonu için İntravitreal Anti-Vasküler Endotelyal Büyüme Faktörü İnjeksiyonu ile Tedavi Edilen Gözlerde Göz İçi Basınç Değişiklikleri: Gerçek Dünya Sonuçları

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ABSTRACT

Purpose: We aimed to evaluate the long-term IOP changes after intravitreal anti-vascular endhotelial growth factor (anti-VEGF) agents (bevacizumab-ranibizumab-aflibercept) with comparing the agents each other.

Method: A retrospective, comparative study was designed to assess the outcome of intravitreal anti-VEGF therapy on IOP. The medical charts of patients treated with intravitreal anti-VEGF (bevacizumab-ranibizumab-aflibercept) for age-related macular degeneration (AMD) from January 2012 to March 2017 were retrospectively reviewed. Patients with any other history of primary open angle glaucoma, pseudoexfoliation syndrome, steroid therapy, intraocular surgery except cataract surgery and patients with the complications such as endophthalmitis, traumatic cataract after intravitreal anti-VEGF injection and with a follow-up shorter than 6 months were excluded. Two groups were defined for the primary endpoint of this study. Patients with IOP elevation ≥6 mmHg and final IOP <21 mmHg were defined as group 1 and patients with IOP elevation ≥6 mmHg and final IOP >21 mmHg were defined as group 2.

Results: 7.2% of all patients had a significant IOP elevation. Patients included in group 1 was significantly higher in the bevacizumab group than in the ranibizumab and aflibercept groups (p=0.041 and p=0.038, respectively). The number of patients included in group 2 although not statistically significant was higher in the bevacizumab group than in the ranibizumab and aflibercept groups (p=0.21 and p=0.13, respectively). In regression analysis, a positive relationship between mean injection number and IOP elevation was shown in bevacizumab group. (p:0.001-adjusted R square 0.63)

Conclusion: The results of this study show that bevacizumab therapy can cause a significant IOP elevation, and its effect on the IOP was stronger than that of aflibercept and ranibizumab. The clinicians should try to keep the number of injections to a minimum, especially for patients with glaucoma histories. We also suggest that ranibizumab and aflibercept might be a clinician's first choices, especially in a patient with a history of glaucoma.

Keywords: Intraocular pressure, anti-vascular endhotelial growth factor therapy, bevacizumab, ranibizumab, aflibercept.

ÖZ

Amaç: İntravitreal anti-vasküler endotelyal büyüme faktörü (anti-VEGF) tedavisini takiben uzun dönem göz içi basınç (GİB) değişikliklerinin değerlendirilmesi ve farklı anti-VEGF ajanların birbirleri ile karşılaştırılması amaçlandı.

Yöntem: GİB üzerine intravitreal anti-VEGF tedavisinin sonuçlarını değerlendirmek üzere retrospektif, karşılaştırmalı bir çalışma tasarlandı. Ocak 2012'den Mart 2017'ye kadar yaşa bağlı maküla dejenerasyonu (AMD) için intravitreal anti-VEGF (bevacizumab-ranibizumab-

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aflibercept) ile tedavi edilen hastaların tıbbi tabloları geriye dönük olarak incelendi. Primer açık açılı glokom, psödoeksfoliasyon sendromu, steroid tedavisi, katarakt cerrahisi haricindeki göziçi cerrahisi ve intravitreal anti-VEGF enjeksiyonu sonrası endoftalmi, travmatik katarakt gibi komplikasyonları olan ve 6 aydan daha kısa süre takip edilen hastalar dışlandı. Çalışmanın hedefi için iki grup tanımlandı. GİB artışı ≥6 mmHg ve son GİB <21 mmHg olan gözler grup 1, GİB artışı ≥6 mmHg ve final GİB> 21 mmHg olan gözler grup 2 olarak tanımlandı.

Bulgular: Hastaların% 7.2'sinde anlamlı GİB yükselmesi saptandı. Bevacizumab uygulanan gözlerden grup 1 e dahil olan olguların ranibizumab ve aflibercept gruplarına göre anlamlı derecede yüksek olduğu görüldü (sırasıyla p = 0.041 ve p = 0.038). Bevacizumab uygulanan gözlerde istatistiksel olarak anlamlı olmamasına rağmen grup 2 ye dahil olan hasta sayısının ranibizumab ve aflibercept gruplarına göre daha yüksek olduğu saptandı. (sırasıyla p = 0.21 ve p = 0.13). Regresyon analizinde bevacizumab grubunda ortalama enjeksiyon sayısı ve GİB yükselmesi arasında pozitif bir ilişki gösterildi. (p: 0.001- adjusted R square= 0.63)

Sonuç: Bu çalışmanın sonuçları, bevacizumab tedavisinin anlamlı bir GİB yükselmesine neden olabileceğini ve GİB üzerindeki etkisinin aflibercept ve ranibizumab'ınkinden daha güçlü olduğunu göstermektedir. Klinisyenler özellikle glokom öyküsü olan olgularda intravitreal enjeksiyon endikasyonunu daha sınırlı tutmaya çalışmalı ve ranibizumab ile aflibercepti öncelikli olarak tercih etmelidir.

Anahtar Sözcükler: Göz içi basınç, anti-vasküler endotelyal büyüme faktörü,bevacizumab, ranibizumab, aflibercept.

INTRODUCTION

An increased level of vascular endothelial growth factor (VEGF) can contribute to the pathogenesis of ocular diseases, like neovascular age-related macular degeneration (AMD), retinal vein occlusion, and diabetic retinopathy.[1] Several therapeutic substances targeted against VEGF (anti-VEGF) have been used to treat these pathologies.[1, 2] For example, there are 3 anti-VEGF agents used for the treatment of AMD and other retinal vascular disorders, with important differences between these agents. Pegaptanib (Macugen; EyeTech Pharmaceuticals, New York, NY, USA) is a ribonucleic acid aptamer that blocks the main pathological isoform of VEGF (VEGF165), while ranibizumab (Lucentis; Novartis, Basel, Switzerland, Genentech, San Francisco, CA, USA, and Roche, Basel, Switzerland) is an affinity matured, humanized, monoclonal fragment of an anti-VEGF antibody, and bevacizumab (Avastin; Genentech and Roche) is a full-length, humanized, monoclonal anti-VEGF antibody.[1,2] Both of ranibizumab and bevacizumab function by blocking the receptor binding domains of all isoforms of VEGF-A.[1,2] Recently, a new anti-VEGF agent called aflibercept (Eylea; Regeneron Pharmaceuticals, Tarrytown, NY, USA and Bayer, Berlin, Germany) has also become an important option for these patients.[1,3] Aflibercept is a fusion protein with binding domains from native VEGF receptors, and it binds to all VEGF-A and VEGF-B isoforms and placental growth factors 1 and 2 with high affinity.[3]

These agents were shown to be efficacious, with rarely reported ocular adverse events; however, the duration of action is limited, and the pathology is not typically cured by a single anti-VEGF treatment.[4-7] Additionally, sustained intraocular pressure (IOP) elevations as a complication of anti-VEGF injections were not reported in the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) trial, Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA), and Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration (VIEW 1 and VIEW 2) study.[4-6] However, recent studies have reported a sustained elevation in the IOP after anti-VEGF treatment.[8-14] Although there have been previous studies using ranibizumab and bevacizumab, to the best of our knowledge, there are only two studies evaluating the effects of aflibercept on the IOP.[15,16] Therefore, we aimed to evaluate the long-term IOP changes after the use of intravitreal anti-VEGF agents (bevacizumab, ranibizumab, and aflibercept), while comparing these agents with each other.

METHODS

A retrospective, comparative study was designed to assess the outcomes of intravitreal anti-VEGF therapy on the IOP. The medical charts of patients treated with bevacizumab, ranibizumab, and aflibercept for AMD from January 2012 to March 2017 were retrospectively reviewed. We excluded patients with any history of primary open angle glaucoma, pseudoexfoliation sydrome, steroid therapy, intraocular surgery (except cataract surgery), complications (such as endophthalmitis or traumatic cataracts) after the intravitreal anti-VEGF injection, and follow-ups shorter than 6 months. Patients treated with anti-VEGF agents for diabetic macular edema and/or retinal vein occlusions are also excluded.

The consent of the local ethics committee was obtained for this study, and this research was conducted in accordance with the Declaration of Helsinki. Before administering the intravitreal anti-VEGF injection, all patients were informed in detail about the side effects of the drug and its administration, and their consent was obtained.

Each injection was administered in an operating room under topical anesthesia using 0.5% proparacaine hydrochloride (Alcaine eye drop; Alcon, Texas, USA) by the same person (EU). Then, a 5% povidone iodine solution was used for the conjunctival irrigation, and the anti-VEGF agent injection (repackaged 1.25 mg/0.05 ml bevacizumab, 0.5 mg/0.05 ml ranibizumab, or 2 mg/0.05 ml aflibercept) was administered via the pars plana, 3.5-4 mm posterior to the limbus, using a syringe with a 30 gauge needle. After the procedure, moxifloxacin eye drops (Vigamox eye drop; Alcon, Texas, USA) were used 4 times daily for 5 days. The IOP measurements were performed by the same person using a

Goldmann applanation tonometer before the injection, the first day after the injection, and at the first week and first month follow-up visits. The baseline IOP was defined as the preinjection mean IOP for two consecutive visits before the first injection, and the final IOP was defined as the mean IOP for two consecutive visits measured the first week and first month after the last injection. The basic demographic information, data obtained via a full ophthalmic examination at each visit (including best corrected visual acuity tests, IOP measurements, slit-lamp examinations, fundus biomicroscopy, and optical coherence tomography), and the total number of bevacizumab, ranibizumab, and aflibercept injections were recorded.

Two groups were defined for the primary endpoint of this study. Patients with IOP elevation ≥6 mmHg and final IOP <21 mmHg were defined as group 1 and patients with IOP elevation ≥6 mmHg and final IOP >21 mmHg were defined as group 2.

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 11.5 for Windows. The Kolmogorov-Smirnov test was used to determine whether the continuous and categorical variables were normally distributed. In addition, the Mann-Whitney U, Kruskal-Wallis, Pearson's chi-squared, likelihood ratio, Wilcoxon signed rank, McNemar, and paired samples t tests were employed when necessary. A p value < 0.05 was considered to be significant.

RESULTS

After the medical records of 750 patients were reviewed, 152 eyes of 122 patients were involved in this study. The demographic characteristics of the patients are presented in Table 1.

The demographic characteristics of different anti-VEGF agents (ranibizumab-bevacizumab-aflibercept) are similar (Table 2). The baseline and final IOP values of the three anti-VEGF agents show no differences (Table 2). Additionally the mean number of injections of the agents were similar (Table 2).

After analyzing all patients treated with anti-VEGF, 7.2% of all patients had a significant IOP elevation. The patients with IOP elevations higher than 6 mmHg with a final IOP<21 mmHg (group 1) were analyzed, and the number of these patients was significantly higher in the bevacizumab group than in the ranibizumab and aflibercept groups (p=0.041 and p=0.038, respectively) (Table 3). Additionally, the number

Table 1. *Demographic and Clinical Characteristics*

Parameters	Values	Range
Mean Age(y)	70.4±11.7	44-93
Mean Follow-up Time(m)	22.3 ± 15.0	6-50
Mean number of injection	4.96±2.2	3-12
AMD	152	
Only Ranibizumab (E)	70(46.05%)	
Only Bevacizumab (E)	39 (25.6 %)	
Only Aflibercept (E)	43 (28.2%)	
Pseudophakia	41 (27.5%)	

AMD: age related macular degeneration y: year m: month E: Eye

Table 2. *Comparison Of Different Anti-VEGF Groups*

	Only Aflibercept	Only Ranibizumab	Only Bevacizumab
Age	72.3±8.3[a,b]	74.1± 7.7[a,c]	69.7±10.8[b,c]
Follow-up	20.0±18.5[a,b]	21.8±9.8[a,c]	25.6±17.9[b,c]
Mean Number of Injection	5.1±2.46 [a,b]	4.8±2.1 [a,c]	5.05±2.02 [b,c]
Baseline IOP	16.2±2.7[a,b]	15.7±2.2[a,c]	15.3±2.2[b,c]
Final IOP	15.8±2.4[a,b]	16.1±2.4[a,c]	15.9±2.6[b,c]

Oneway Anova (Post Hoc Tamhane) a. The difference between aflibercept and ranibizumab group was statistically not significant (p=0.43, for age, p=0.51 for follow-up, p=0.59, for mean number of injection, p=0.48, for baseline IOP, p=0.56, for final IOP), b: The difference between aflibercept and bevacizumab group was statistically not significant (p=0.13, for age, p=0.17 for follow-up, p=0.29, for mean number of injection, p=0.09, for baseline IOP, p=0.69, for final IOP), c: The difference between ranibizumab and bevacizumab group was statistically not significant (p=0.09, for age, p=0.27 for follow-up, p=0.19, for mean number of injection, p=0.14, for baseline IOP, p=0.38, for final IOP)

Table 3. *Comparisons According to the Definition of Significant Intraocular Pressure Elevation*

Parameters	Only Aflibercept	Only Ranibizumab	Only Bevacizumab
Patients	43	70	39
Group 1	2,3% [a,b] (1)	2,8% [a,d] (2)	12,8% [b,d] (5)
Group 2	0% [a,c] (0)	1,4% [a,e] (1)	5,1% [c,e] (2)

Pearson chi-square test IOP: intraocular pressure a. The difference between aflibercept and ranibizumab group was statistically not significant (p=0.87, group1, p=1.0, group 2), b: The difference between aflibercept and bevacizumab group was statistically significant for group 1 (p=0.038, group 1) c: The difference between aflibercept and bevacizumab group was statistically not significant for group 2 (p=0.13, group 2), d: The difference between ranibizumab and bevacizumab group was statistically significant for group 1(p=0.041,group 1), e: The difference between ranibizumab and bevacizumab group was statistically not significant for group 2 (p=0.21,group 2)

of patients with IOP elevations higher than 6 mmHg with a final IOP>21 mmHg (group 2) although not statistically significant was higher in the bevacizumab group than in the ranibizumab and aflibercept groups (p=0.21 and p=0.13, respectively). (Table 3). The patients involved in group 1 and group 2 had mean injections of 9±2.8, 8.75±1.7, and 7.25 ±3.2 for aflibercept, ranibizumab and bevacizumab respectively.

In the regression analysis, a positive relationship between the mean injection number and IOP elevation was seen in the bevacizumab group (p=0.001, adjusted R square 0.63). However, the same relationship was not shown for the aflibercept and ranibizumab groups (p=0.052 and p=0.058, respectively). Moreover, in the univariate analysis, the age, sex, and diagnosis were not related to the IOP elevation (p=0.281, p=0.358, and p=0.824 for the aflibercept group, p=0.598, p=0.487, and p=0.244 for the ranibizumab group, and p=0.290, p=0.485, and p=0.340 for the bevacizumab group, respectively). Additionally pseudophakia was not found to affect the IOP elevation in the univariate analysis (p=0.47 for aflibercept, p=0.69 for ranibizumab, and p=0.38 for bevacizumab). Three patients in the bevacizumab group and one patient in the ranibizumab group required antiglaucomatous therapy.

DISCUSSION

Several therapeutic agents have been shown to be efficacious in the treatment of AMD, retinal vein occlusion, and diabetic retinopathy, with rarely reported ocular adverse events; however, the duration of action is limited, and the pathology is not typically cured by a single anti-VEGF treatment.[4-7] In addition, a sustained IOP elevation as a complication after anti-VEGF injections was not reported in the ANCHOR, MARINA, and VIEW 1 and VIEW 2 trials.[4-6] However, recent studies have reported a sustained IOP elevation after multiple anti-VEGF injections.[8-14]

Hollands et al.[17] showed that the IOP elevation normalized within 2 hours in 103 of 104 patients after an intravitreal injection of bevacizumab, but there have been several reports showing sustained IOP elevations.[8-12,18-15,16] In one study, the sustained IOP elevation was defined as an IOP greater than 22 mmHg, with a baseline of greater than 6 mmHg, and lasting for 30 days including at least two visits. In that study, Good et al.[10] reported a sustained IOP elevation rate in 10 of 101 (9.9%) eyes treated with bevacizumab and 3 of 96 (3.1%) eyes treated with ranibizumab. Similarly, Kim et al.[18] and Baek et al.[20] presented rates of sustained IOP elevation of 3.5% and 5.9%, respectively. Additionally, Freund et al.[15] reported rates of an IOP elevation higher than 10 mmHg of 3.2% through week 52 and 6.4% through week 96 in patients treated with ranibizumab. They also reported a low incidence of IOP increases in the aflibercept group, which was notably higher in the ranibizumab group.[15] Furthermore, Rusu et al.[16] reported that the intraocular pressure was significantly lower in patients switched to aflibercept after previous treatments with ranibizumab and/or bevacizumab.

The previous studies have presented varying results because of their different definitions of an IOP elevation. In the present study, we defined two groups. Group 1 involves the patients with IOP elevations higher than 6 mmHg with a final IOP<21 mmHg Group 2 involves the patients with IOP elevations higher than 6 mmHg with a final IOP>21. After analyzing the results of the patients, we found that 7.2% of all patients had significant IOP elevations (Table 3), which is consistent with the literature.[8,10-12] The number of patients involved in group 1 was significantly higher in the bevacizumab group (12.8%) than in the ranibizumab (2.8%) and aflibercept groups (2.3%). The rates of the patients involved in group 1 were 2.8% in the ranibizumab group and 2.3% in the aflibercept group (Tables 3), but these proportions are lower than those in the literature.[10,11,15,21,22] The lower number of injections and the limited number of eyes included in both of our groups when compared with the literature could be the result of this difference.[10,11,15,21,22] Additionally, the number of patients involved in group 2 were also analyzed. There were no differences between the three anti-VEGF agents.(ranibizumab, bevacizumab and aflibercept). (Table 3). The limited number of our patients could cause this result.

The most common theory explaining the pathogenesis of a sustained IOP elevation is the microparticle obstruction of the trabecular meshwork,[23] and it has been suggested

that bevacizumab is approximately three times larger than ranibizumab (149 kDa versus 48 kDa); therefore, it seems that bevacizumab may be more likely to obstruct the outflow channels.[9,11] Additionally, Kahook et al.[24] showed that different samples of repackaged bevacizumab included various concentrations of high molecular weight protein aggregates. We believe that our results from the bevacizumab group support this literature.

However, although the IOP elevation values were lower in the aflibercept group, we found that there were no significant differences between the ranibizumab and aflibercept groups in terms of group 1 and group 2. This finding is not consistent with the literature.[15,16] For example, Freund et al.[15] reported that the incidence of IOP elevation in eyes treated with aflibercept was lower than in those treated with ranibizumab. Although the aflibercept molecules are larger than the ranibizumab molecules (115 kDa compared to 48 kDa, respectively), they suggested that the glycosylation of aflibercept may improve solubility in the vitreous, when compared with ranibizumab, and prevent the potential microparticle accumulation, which is the most common theory explaining the pathogenesis of a sustained IOP elevation.[15,25,26]

A correlation between the mean number of injections and the IOP elevation has been reported by previous studies.[19,20] Hoang et al.[19] presented a positive correlation between the number of injections and the continuous elevation of the IOP. In addition, Baek et al. suggested that multiple intravitreal injections could be associated with a sustained IOP elevation.[20]

In the present study, the significant IOP elevation was seen in patients treated with six or more injections. Additionally, a positive correlation between the mean injection number and IOP elevation was shown in the bevacizumab group (p=0.001, adjusted R square 0.63); however, the same correlation was not shown for the aflibercept and ranibizumab groups (p=0.052 and p=0.058, respectively). The lower rates of significant IOP elevation in ranibizumab and bevacizumab groups could be the reason of this result.

Similar to the literature,[20] we determined that the age, sex, and diagnosis were not related to the IOP elevation in all three anti-VEGF groups (p=0.281, p=0.358, and p=0.824 for aflibercept, p=0.598, p=0.487, and p=0.244 for ranibizumab, and p=0.290, p=0.485, and p=0.340 for bevacizumab, respectively).

Previous studies have shown an association between pseudophakia and a sustained IOP elevation.[21,27] Moreover, pharmacokinetic reports have suggested that pseudophakic patients, especially those who have had Nd:YAG capsulotomies, are more prone to having a sustained IOP elevation.[28] They argued that there may be a disruption of the anterior hyaloid or zonules, allowing anti-VEGF agent particles access to the anterior chamber.[10,11] However, in the present study, pseudophakia was not found to affect the IOP elevation in the univariate analyses.

In the present study, three patients in the bevacizumab group and one patient in the ranibizumab group required antiglaucomatous therapy. None of the patients required surgery for the treatment of glaucoma, and none of the patients had histories of glaucoma or PSX.

The most important limited factor of this study was the insufficient number of patients. The comparisons of three different agents could be influences by number of anti-VEGF injections and patients.

CONCLUSION

The results of this study show that bevacizumab therapy can cause a significant IOP elevation, and its effect on the IOP was stronger than that of aflibercept and ranibizumab. Additionally, we presented an association between the number of injections and an IOP elevation. Therefore, we recommended that clinicians consider the possibility of a sustained IOP elevation when there is a history of multiple intravitreal anti-VEGF injections. They should try to keep the number of injections to a minimum, especially for patients with glaucoma histories. We suggest that ranibizumab and aflibercept might be a clinician's first choices, especially in a patient with a history of glaucoma.

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