Sustained Elevation of Intraocular Pressure After Multiple Intravitreal Antivascular Endothelial Growth Factor Injection Agents: Comparison of Bevacizumab and Ranibizumab

Çoklu Intravitreal Antivasküler Endotelyal Büyüme Faktörü Enjeksiyonu Sonrası Göz İçi Basıncında Devamlılık Gösteren Artış: Bevacizumab ile Ranibizumabın Karşılaştırılması

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ABSTRACT

Purpose: To evaluate the long-term intraocular pressure (IOP) changes after intravitreal bevacizumab and ranibizumab and to compare their impacts on IOP.

Method: The medical charts of patients treated with intravitreal anti-vascular endothelial growth factor anti-vascular endothelial growth factor (VEGF) (bevacizumab-ranibizumab) for retinal vascular disorders or age-related macular degeneration (AMD) from January 2011 to January 2015 were retrospectively reviewed. Patients with any other history of steroid therapy and intraocular surgery except cataract surgery were excluded. Baseline IOP was defined as the pre-injection 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 at first month after the last injection. Significant IOP elevation was defined as IOP elevation higher than 5 mmHg or final IOP higher than 21 mmHg provided that it is higher than baseline IOP.

Results: Hundred eighty three eyes (143 with AMD and 40 with diabetic macular oedema) from 160 patients were included in this study. IOP elevation after intravitreal anti-VEGF therapy was statistically significant (P=0,0001 paired samples t-test). Sixteen eyes (8.7%) had IOP elevations greater than 5 mmHg, Ten (5.4%) had final IOPs higher than 21 mmHg. After the exclusion of patients with primary open angle glaucoma (PAOG) and pseudoexfoliation syndrome (PXS), two of 132 eyes in the ranibizumab group and two of 22 eyes in the bevacizumab group had final IOP values higher than 21 mmHg. The differences were statistically significant (p=0.040, Pearson chi-square test).

Conclusion: IOP rise is more significant in patients who received bevacizumab compared to ranibizumab. Hence ranibizumab injection might be recommended as a first choice especially in patients with POAG.

Key Words: Vascular endothelial growth factor, ranibizumab, bevacizumab, intraocular pressure.

ÖZ

Amaç: İntravitreal bevacizumab ve ranibizumab tedavisini takiben izlenen uzun dönem göz içi basıncı (GİB) değişikliklerinin araştırılması ve iki ajanın karşılaştırılması

Gereç ve Yöntem: Ocak 2011 ile Ocak 2015 tarihleri arasında retinal vasküler hastalık veya yaşa bağlı makula dejenerasyonu (YBMD) tedavisinde intravitreal anti-vasküler endotelyal büyüme faktörü (VEGF) uygulanmış hastaların dosyaları retrospektif şekilde tarandı. Öyküsünde katarakt cerrahisi dışında intraoküler cerrahi ve steroid tedavisi olan hastalar çalışma dışında bırakıldı. Bazal GİB ilk enjeksiyon öncesi iki ardışık vizitte ölçülen GİB' nın ortalaması şeklinde tanımlanırken, final GİB ise son enjeksiyonun birinci ayında iki ardışık vizitte ölçülen orta-

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lama GİB'nın ortalaması şeklinde tanımlandı. GİB'da 5 mm Hg'dan daha fazla artış olması veya final GİB 21 mmHg üzerinde olması anlamlı GİB artışı şeklinde kabul edildi.

Bulgular: 160 hastanın 183 gözü (143 YBMD, 40 diyabetik makula ödemi) çalışmaya dahil edildi. Anti-VEGF tedavi sonrası GİB'daki yüksel istatiksel anlamlı bulundu (P=0.0001 paired samples t-test). 183 gözden 16 sında (%8.7) GİB artışı 5 mmHg den fazla idi, 10 gözde (%5.4) final GİB 21 mm Hg üzerinde idi. Primer açık açılı glokom (PAAG) ve psödoeksfoliatif sendrom (PES) tanısı olan olgular dışlandığında ranibizumab grubunda 132 gözden ikisinde, bevacizumab grubunda 22 gözden ikisinde final GİB 21 mmHg üzerinde idi. İki grup arasındaki fark istatiksel olarak anlamlıydı (p=0.040, Pearson ki-kare test).

Sonuç: Bu çalışma, bevacizumab tedavisinin GİB düzeyini ranibizumab'dan daha fazla artırdığını göstermektedir, bu nedenle özellikle PAAG olgularında ranibizumabın öncelikli tercih olması önerilebilir.

Anahtar Kelimeler: Vasküler endotelyal büyüme faktörü, ranibizumab, bevacizumab, göz içi basıncı.

INTRODUCTION

Vascular endothelial growth factor (VEGF) is an important factor in the pathogenesis of retinal vascular disorders, such as age-related macular degeneration (AMD), retinal vein occlusion and diabetic retinopathy (DRP).[1] Therefore, anti-VEGF agents are the mainstay of treatment for such diseases. Intravitreal ranibizumab (Lucentis; Genentech, San Francisco, CA) and bevacizumab (Avastin; Genentech) are anti-VEGF agents used to treat retinal vascular disorders.[2,3] Although these agents have been shown to be efficacious with rarely reported ocular adverse events, their duration of action is limited, and the pathology is typically not cured by a single anti-VEGF treatment.[2-4] A transient increase in intraocular pressure (IOP) can occur after the injection of fluid into the vitreous cavity. Elevated IOP as a complication following anti-VEGF injections was not reported in two trials: "Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration" (ANCHOR) and "Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration" (MARINA).[2,3] However, recent studies have suggested sustained elevations in IOP after anti-VEGF treatment.[5-11] Good et al.[7] showed sustained IOP elevations in 6% of all studied eyes (215) and in 33% of the study patients with previously diagnosed glaucoma. Additionally, they found a higher prevalence of elevated IOP in eyes treated with bevacizumab alone (9.9%) than in those treated with ranibizumab alone (3.1%).[7] Similarly, Adelman et al.[8] showed that four out of 116 patients with AMD (3.45%) developed sustained elevations in IOP after anti-VEGF therapy.

In the present study, we aimed to evaluate and compare long-term IOP changes after the administration of intravitreal bevacizumab and ranibizumab.

MATERIALS AND METHODS

The study protocol was approved by the Institutional Review Board/Ethics Board of Gazi University. A retrospective, comparative study was designed to assess the effects of intravitreal anti-VEGF therapy on IOP. We retrospectively reviewed the medical charts of patients treated with intravitreal anti-VEGFs (bevacizumab or ranibizumab) for retinal vascular disorders or AMD from January 2011 to January 2015. Patients with any other history of steroid therapy, of intraocular surgery except cataract surgery, angle closure glaucoma or of proliferative diabetic retinopathy; patients with complications such as endophthalmitis or traumatic cataract after intravitreal anti-VEGF injection; and patients with follow-up periods shorter than six months were excluded from the study. Eyes treated with both ranibizumab and bevacizumab were also excluded.

Eyes treated with only one type of anti-VEGF (ranibizumab or bevacizumab) with a follow-up period longer than six months were included in the current study. The patients treated in both eyes included in the current study, only if a different type of anti-VEGF treatment was applied to different eyes. Patients with primary open angle glaucoma, pseudoexfoliation syndrome and family history of glaucoma were also included. Statistical analysis was repeated in patients with and without a history of primary-open angle glaucoma, pseudoexfoliation syndrome and family history.

All injections were performed in an operating room under topical anaesthesia, achieved using 0.5% proparacaine hydrochloride (Alcaine; Alcon). After the use of a 5% povidone-iodine solution for irrigation of the conjunctiva, conjunctival displacement was performed with a cotton tip, and the anti-VEGF agent (1.25 mg/0.05 ml repackaged bevacizumab or 0.5 mg/0.05 ml ranibizumab) was injected via the pars plana, 3.5–4 mm posterior to the limbus, using a syringe with a 30-gauge needle. After the procedure, the patients were instructed to use netilmicin eye drops (Netira; Teka Pharma, Turkey) four times daily for three days. IOP was measured with a Goldmann applanation tonometer before injection, the first week after injection, and first-month visits. The measurements were performed between 9 am and 11 am. The baseline IOP was defined as the pre-injection mean IOP for two consecutive visits before the first injection, and the final IOP was defined as the mean IOP for two consecutive visits in the first month after the last injection.

Basic demographic information was recorded, as well as data obtained by full ophthalmic examinations at each visit. These examinations included best corrected visual acuity tests, IOP measurements, slit-lamp examinations, fundus biomicroscopy and optical coherence tomography. The total number of bevacizumab or ranibizumab injections given was also recorded. Significant IOP elevation was defined as being higher than 5 mmHg or as a final IOP higher than 21 mmHg, provided this was higher than the baseline IOP.

The statistical analyses were performed using SPSS for Windows, version 11.5. Paired samples t-tests were used to compare the baseline and final IOP values. Subgroup analyses were done via independent samples t-tests. Pearson correlation and multivariate analyses were performed to assess the relationship between the number of injections given and IOP elevation. A p value of <0.05 was considered statistically significant.

RESULTS

The medical records of 500 patients were reviewed, and 183 eyes (143 with AMD and 40 with diabetic macular oedema) from 160 patients were included in this study. The demographic characteristics of the patients are shown in Table 1.

Table 1. *Demographic Characteristics.*

Parameters	Values	Range
Mean age (y)	71.3±11.1	35-91
Mean follow-up time (m)	21.9 ± 17.0	6-78
Mean number of ranibizumab injection	7.8±5.0	3-24
Mean number of bevacizumab injection	5.0±2.1	3-12
AMD /DME	143/40	
Only ranibizumab (E)	149	
Only bevacizumab (E)	34	
POAG*	9	
PSX*	22	
Family history of glaucoma**	1	
Pseudophakia	49	

AMD: age related macular degeneration
DME: diabetic macula edema y: year
m: month E: Eye POAG: primary open angle glaucoma
PSX: pseudoexfoliation * 2 patients with PSX also have POAG
**This patient has also POAG

The baseline IOP value of all eyes was measured as 14.4±2.7 (8–24 mmHg), and the final IOP value of all eyes was 15.6±2.8 (10–28 mmHg). The IOP elevation was statistically significant (p=0.0001, paired samples t-test) (Table 2). The same analysis was performed after the exclusion of patients with primary open angle glaucoma (POAG) and pseudoexfoliation syndrome (PXS), intended to exclude the effects of glaucomatous diseases on IOP. After these exclusions, the baseline IOP value was 14.6±2.6 mmHg, the final IOP value was 15.6±2.7 mmHg and the IOP elevation was still statistically significant (p=0.0001) (Table 2).

Table 2. *Comparison of Baseline and Final IOP Values.*

Parameters	Baseline IOP	Final IOP	p
All Patients	14.4 ± 2.8	15.6 ±2.8	0.0001*
Patients Without POAG-PSX	14.5±2.7	15.7±2.6	0.0001*

*Paired samples t test POAG: primary open angle glaucoma PSX: pseudoexfoliation

Sixteen eyes (8.7%) from 183 had IOP elevations greater than 5 mmHg. One of these patients had POAG, and two had PXS. Ten (5.4%) of the 183 had final IOPs higher than 21 mmHg; three of these patients had POAG, and three had PXS. The significant IOP elevation rates of the patients with and without POAG and PXS are presented in Table 3. The patients with final IOPs higher than 21 mmHg needed additional antiglaucomatous therapy, and the IOP elevation was successfully treated with medical therapy in all patients. No additional surgical treatment was required.

We also compared patients treated with ranibizumab and bevacizumab after excluding patients with POAG or PXS. Two of 132 eyes in the ranibizumab group and two of 22 eyes in the bevacizumab group had final IOP values higher than 21 mmHg. The differences were statistically significant (p=0.040, Pearson chi-square test). Patients with IOP elevations greater than 5 mmHg were higher in the bevacizumab group than in the ranibizumab group, although this difference was not statistically significant (p=0.090) (Table 4). The mean IOP elevation in the patients treated with bevacizumab was comparable to that in patients treated with ranibizumab (p=0.350, independent samples t-test) (Table 4).

Table 3. *The Significant IOP Elevation Rates of Patients with or without POAG - PSX.*

Parameters	All patients	Patients without POAG and PSX	Patients with POAG	Patients with PSX
Eye	183	154	9	22
Final IOP>21 mmHg	10 (5.4%)	4 (2.5%)	3(33.3%)	3 (13.6%)
Higher 5mmHg	16 (8.7%)	13 (8.4%)	1(11.1%)	2 (9.0%)
Additional therapy	10 (5.4%)	4 (2.5%)	3(33.3%)	3 (13.6%)

POAG: primary open angle glaucoma PSX: pseudoexfoliation 2 patients with PSX also have POAG

Table 4. *Comparison of Patients Treated with Only Bevacizumab to treated with Only Ranibizumab.*

Parameters	Only Bevacizumab	Only Ranibizumab	P
Patients	22	132	
IOP elevation	1.9±2.7	1.3±2.3	0.35*
Final IOP>21 mmHg	2/22	2/132	0.04**
Higher 5mmHg	18.1% (4)	6.8% (9)	0.09**
Mean number of injection	4.9±2.2	7.8±5.0	0.008*
Correlation analysis between Number of injection-EIOP	r= 0.28 p=0.09	r= 0.311 p=0.001	
Univariate analysis (D)	p= 0.76	p= 0.89	
Univariate analysis (S)	p= 0.29	p= 0.155	
Univariate analysis (A)	p= 0.44	p= 0.37	
Univariate analysis (LC)	p= 0.38	p= 0.35	
Univariate analysis number of injection	p= 0.08	p= 0.001	

*independent samples t test **Pearson chi-square test
IOP: Intraocular pressure EIOP: elevation of intraocular pressure
D: diagnosis S: sex A: age LC: lens condition

However, the number of ranibizumab injections given was statistically significantly higher than the number of bevacizumab injections given (p=0.008) (Table 4).

The effects of different factors on IOP were also analysed separately for both the ranibizumab and bevacizumab group. In patients treated with ranibizumab, a Pearson correlation analysis showed a weak positive correlation between the number of injections and elevations in IOP (p=0.001, r=0.311) (Table 4). This correlation was not found in patients treated with bevacizumab (p=0.09, r=0.280) (Table 4). A univariate analysis also showed that the number of injections had a significant effect on the elevation of IOP in patients treated with ranibizumab (p=0.001) but not in patients treated with bevacizumab. Additionally, a multivariate analysis found that age, sex, diagnosis and lens condition had no effect on IOP elevation (Table 4).

We also found that IOP elevation was greater in pseudophakic eyes (1.4±2.3 mmHg) than in phakic eyes (1.25±2.4 mmHg), but the difference was not statistically significant (p=0.300).

DISCUSSION

Anti-VEGF agents have been shown to be efficacious in clinical practice with rarely reported ocular adverse events. They are the mainstay of therapy for retinal vascular diseases and AMD. However, the long-term safety data are still insufficient.[1-3] Short-term transient ocular hypertension immediately after intravitreal anti-VEGF therapy is a well-known complication. While sustained IOP elevations after anti-VEGF injections were not reported in the ANCHOR or MARINA trials,[2,3] recent reports suggest that such elevations are possible.[5-8]

It has been previously reported that immediate elevations in IOP after injection normalize within 30–120 minutes without any lowering therapy.[12-14] Hollands et al.[12] showed that elevations in IOP normalized within two hours in 103 of 104 patients treated with intravitreal injections of bevacizumab, and they suggest that this treatment is safe with respect to short-term IOP changes. However, several reports have indicated sustained IOP elevation.[5-9,15,16] Good et al.[7] reported sustained IOP elevation in 10 eyes among 101 (9.9%) treated with bevacizumab and three eyes among 96 (3.1%) treated with ranibizumab. They defined sustained IOP elevation as an IOP greater than 22 mmHg, with a value above the baseline greater than 6 mmHg, lasting 30 days including at least two visits.[7] Kim et al.[15] also showed sustained IOP elevation in 14 of 401 eyes (3.5%). Similarly, Baek et al.[17] reported an IOP increase greater than 5 mmHg above the baseline in nine eyes of 152 (5.9%) treated with bevacizumab. Other previous studies showed varying results because of differing definitions of IOP elevation. In the present study, we compared baseline IOP values to final IOP values and analysed patients with IOP elevations greater than 5 mmHg and patients with final IOPs higher than 21 mmHg. Subgroup analyses were also done. We included 183 eyes (143 with AMD and 40 with diabetic macular oedema) from 160 patients with a mean follow-up time of 21.9 months (6–78 months). Like previous studies, our study showed that the final IOP values were significantly higher than the baseline IOP values. To exclude the effect of glaucomatous diseases on IOP, we repeated the analysis without patients with POAG or PXS, and we reached the same conclusion. Also like other studies, we found that 13 eyes of 154 (8.4%) had IOP elevations greater than 5 mmHg (Table 3).[7,16-18] Additionally, after excluding patients with POAG and PXS, we found that four eyes of 154 (2.5%) had final IOPs higher than 21 mmHg (Table 3). Agard et al.[19] suggest that the risk of intravitreal-anti-VEGF-induced IOP elevation increases in the presence of glaucoma and must be checked during follow-up. Consistent with this, three of the nine patients in the present study with a history of POAG had a final IOP value higher than 21 mmHg and required additional anti-glaucomatous therapy.

Previous studies reported a correlation between the mean number of injections and IOP elevation. Tseng et al.[9] showed a high proportion of eyes with significant elevations in IOP after a high number (>20) of intravitreal injections. Additionally, Hoang et al.[16] and Baek et al.[17] reported a positive

correlation between the number of injections and sustained elevations in IOP. Similarly, in patients in our study treated with ranibizumab, the univariate analysis showed that the number of injections had a significant effect on elevations in IOP (p=0.001). We also found a weak positive correlation between the number of injections and IOP elevation (p=0.001, r=0.311). The same correlation was not found in patients treated with bevacizumab (p=0.09, r=0.280) (Table 4). We suggest that this could be due to the limited number of patients in the bevacizumab group. Additionally, like Baek et al., we found no association between IOP elevation and age, sex, diagnosis or lens condition in either the ranibizumab or bevacizumab group (Table 4).[17]

Some studies report an association between phakic eyes and sustained IOP elevation.[21,22] However, other reports suggest that sustained elevations in IOP are more common in pseudophakic eyes with a history of neodymium-doped yttrium aluminium garnet laser (Nd:YAG) capsulotomy.[7,8] Pharmacokinetic studies also report that pseudophakic patients, especially those who have had a Nd:YAG capsulotomy, are prone to sustained elevations in IOP,[23] as there may be a disruption of the anterior hyaloid or zonules, allowing anti-VEGF agent particles into the anterior chamber.[7,8] We also found that IOP elevation was greater in pseudophakic eyes, although the difference was not statistically significant (p=0.300). We suspect that the low rate of Nd:YAG treatment in our pseudophakic patients may be the cause of this insignificant difference.

There are multiple theories explaining the pathogenesis of sustained elevations in IOP, but the most common theory is microparticle obstruction of the trabecular meshwork.[20] Kahook et al.[24] showed that multiple samples of repackaged bevacizumab included various concentrations of high-molecular-weight protein aggregates. Additionally, Good et al.[7] reported that a high proportion of patients with sustained elevations in IOP received intravitreal injections from the centre obtaining repackaged bevacizumab. We showed that two of 132 eyes in the ranibizumab group and two of 22 eyes in the bevacizumab group had final IOP values higher than 21 mmHg. The difference between the ranibizumab and bevacizumab groups was statistically significant (p=0.04, Pearson chi-square test). We also found that, compared to the ranibizumab group, the bevacizumab group had greater IOP elevations and a higher number of patients with IOP elevations greater than 5 mmHg, although the differences were not statistically significant. We suggest that the insignificance of the differences may be due to the fact that the number of injections was significantly higher in the ranibizumab group and to the limited number of patients in the bevacizumab group. The patients treated only with bevacizumab had an 18.1% rate of IOP elevations greater than 5 mmHg. This proportion is higher than that reported in the literature.[7,8,25] This difference could be due to the limited number of patients in our bevacizumab group and the use of repackaged bevacizumab. As in other reports, patients treated only with ranibizumab had a 6.8% rate of IOP elevations greater than 5 mmHg.[7,8,22] It has been suggested that because bevacizumab (150 kDa) is approximately three times larger than ranibizumab (48 kDa), bevacizumab may be more likely to obstruct outflow channels.[6,8] Our report seems to support this suggestion. We recommend that ranibizumab be the first treatment choice for retinal vascular disorders and AMD, especially in patients with POAG.

Our study's most important limitation is its retrospective design. The number of patients treated only with bevacizumab is also limited. Another weakness of this study format is the lack of a control group.

Our report shows that after anti-VEGF injections, the final IOP values were significantly higher than the baseline IOP values, and 13 eyes of 154 (8.4%) had IOP elevations greater than 5 mmHg. These results are similar to those in the literature. We also showed that patients with POAG tend to develop sustained IOP elevations; hence, these patients must be followed closely. Our study's univariate analysis showed that the number of injections had a significant effect on IOP elevation (p=0.001); thus, clinicians must consider the increased possibility of sustained IOP elevation in patients with a history of multiple intravitreal anti-VEGF injections. Because the rate of high IOP values was significantly greater in the bevacizumab than in the ranibizumab group, we recommend that ranibizumab be the clinician's first treatment choice, especially in patients with POAG. There remains a need for extensive prospective clinical studies comparing the impacts of different anti-VEGF agents on IOP.

REFERENCES / KAYNAKLAR

1. Kliffen M, Sharma HS, Mooy CM, et al. Increased expression of angiogenic growth factors in age-related maculopathy. Br J Ophthalmol 1997;81:154–62.
2. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–31.
3. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432–44.
4. Research Group CATT. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;364:1897–1908
5. Kahook MY, Kimura AE,Wong LJ, et al. Sustained elevation in intraocular pressure associated with intravitreal bevacizumab injections. Ophthalmic Surg Lasers Imaging 268 2009;40:293–5.
6. Bakri SJ, McCannel CA, Edwards AO et al. Persistent ocular hypertension following intravitreal ranibizumab. Graefes Arch Clin Exp Ophthalmol 2008;246:955–8.

7. Good TJ, Kimura AE, Mandava N, et al. Sustained elevation of intraocular pressure after intravitreal injections of anti-VEGF agents. Br J Ophthalmol 2011;95:1111–4.

8. Adelman RA, Zheng Q, Mayer HR. Persistent ocular hypertension following intravitreal bevacizumab and ranibizumab injections. J Ocul Pharmacol Ther 2010;26:105–10.

9. Tseng JJ, Vance SK, Della Torre KE, et al. Sustained increased intraocular pressure related to intravitreal antivascular endothelial growth factor therapy for neovascular age-related macular degeneration. J Glaucoma 2012;4:241–7.

10. Loukianou E, Brouzas D, Apostolopoulos M. Sustained ocular hypertension following intravitreal injections of 0.5 mg/0.05 ml ranibizumab. Int Ophthalmol 2011;31:211–3.

11. Choi D, Ortube M, McCannel C, et al. Sustained elevated intraocular pressures after intravitreal injection of bevacizumab, ranibizumab, and pegaptanib. Retina 2011;31:1028–35.

12. Hollands H, Wong J, Bruen R, et al. Short-term intraocular pressure changes after intravitreal injection of bevacizumab. Can J Ophthalmol 2007;42:807–11.

13. Kim JE, Mantravadi AV, Hur EY et al. Short-term intraocular pressure changes immediately after intravitreal injections of anti-vascular endothelial growth factor agents. Am J Ophthalmol 2008;146:930–41.

14. Bakri SJ, Pulido JS, McCannel CA, et al. Immediate intraocular pressure changes following intravitreal injections of triamcinolone, pegaptanib, and bevacizumab. Eye (Lond) 2009;23:181–5.

15. Kim YJ, Sung KR, Lee KS, et al. Long-term effects of multiple intravitreal antivascular endothelial growth factor injection on intraocular pressure. Am J Ophthalmol 2014;157:1266–71.

16. Hoang QV, Mendonca LS, Della Torre KE, et al. Effect on intraocular pressure in patients receiving unilateral intravitreal anti-vascular endothelial growth factor injections. Ophthalmology 2012;119:321–6.

17. Baek SU, Park IW, Suh W. Long-term intraocular pressure changes after intravitreal injection of bevacizumab. Cutan Ocul Toxicol. 2016;35(4):310-4.

18. Freund KB, Hoang QV, Saroj N et al. Intraocular Pressure in Patients with Neovascular Age-Related Macular Degeneration Receiving Intravitreal Aflibercept or Ranibizumab. Ophthalmology. 2015;122(9):1802-10.

19. Agard E, Elchehab H, Ract-Madoux G et al. Repeated intravitreal anti-vascular endothelial growth factor injections can induce iatrogenic ocular hypertension, especially in patients with open-angle glaucoma. Can J Ophthalmol. 2015;50(2):127-31.

20. Dedania VS, Bakri SJ Review: Sustained Elevation Of Intraocular Pressure After Intravitreal Anti-Vegf Agents: What Is the Evidence? Retina. 2015;35(5):841-58.

21. Pershing S, Bakri SJ, Moshfeghi DM. Ocular hypertension and intraocular pressure asymmetry after intravitreal injection of anti-vascular endothelial growth factor agents. Ophthalmic Surg Lasers Imaging Retina 2013;44:460–4.

22. Hoang QV, Tsuang AJ, Gelman R, et al. Clinical predictors of sustained intraocular pressure elevation due to intravitreal antivascular endothelial growth factor therapy. Retina 2013;33: 179–87.

23. Krohne TU, Eter N, Holz FG et al. Interocular pharmacokinetics of bevacizumab after single use intravitreal injections in humans. Am J Ophthalmol 2008;146:508–12.

24. Kahook MY, Liu L, Ruzycki P et al. High-molecular-weight aggregates in repackaged bevacizumab. Retina 2010; 30:887–92.

25. Mathalone N, Arodi-Golan A, Sar A, et al. Sustained elevation of intraocular pressure after intravitreal injections of bevacizumab in eyes with neovascular age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 2012;250:1435–40.