Original Article

Long-term effect of anti-vascular endothelial growth factor injections on intraocular pressure

Ashiyana Nariani, Blake Williams, Seenu M Hariprasad

Objective: There is a substantial debate in the ophthalmology community about whether anti-vascular endothelial growth factor (VEGF) injections result in a long-term increase in intraocular pressure (IOP). **Design:** We performed a retrospective study to investigate how the number and timing of intravitreal injections in patients with age-related macular degeneration (AMD) and diabetic macular edema (DME) affect IOP over time. **Methods:** We collected long-term IOP data on patients receiving anti-VEGF injections at our institution. Patients over the age of 40 years who received injections for AMD ($n = 76$) or DME ($n = 55$) were included. Patients were grouped according to indication as well as number of injections received (1–3, 4–6, 7–9, or 10+ injections). IOP measurements were then placed into time points (0–6, 6–12, 12–18, 18–24, or 24+ months) and compared to the preinjection average IOP. **Results:** For patients with DME, average preinjection IOP was 15.7 mmHg. At 24+ months after injection, the average IOP was 15.2 ($P = 0.68$) for patients receiving 1–3 injections, 16.8 ($P = 0.23$) for 4–6 injections, and 14.4 ($P = 0.66$) for 7–9 injections. For patients with AMD, average initial IOP was 15.6 mmHg. At 24+ months after injection, the average IOP was 12.6 ($P = 0.97$) for 1–3 injections, 14.9 ($P = 0.96$) for 4–6 injections, 14.8 ($P = 0.84$) for 7–9 injections, and 15.7 ($P = 0.56$) for 10+ injections. **Conclusions:** There was no increase in IOP over time for AMD or DME patients, regardless of how many injections they received. For patients receiving unilateral injections, there was no increase in IOP in the injected eye when compared to the noninjected eye.

Key words: Age-related macular degeneration, diabetic macular edema, intraocular pressure, intravitreal anti-vascular endothelial growth factor injections

Access this article online

Website: www.ijo.in

DOI: 10.4103/0301-4738.194329

Quick Response Code:

Vascular endothelial growth factor (VEGF) serves important roles in ocular homeostasis and is produced by a variety of cell types.[1] An increased level of VEGF can lead to ocular pathology that can be counteracted by intravitreal anti-VEGFs such as ranibizumab (Lucentis; Genentech, San Francisco, California), aflibercept (Eylea; Regeneron, Tarrytown, New York, USA), and bevacizumab (Avastin; Genentech, San Francisco, California). Anti-VEGF injection therapy is widely used to treat a variety of retinochoroidal disorders such as age-related macular degeneration (AMD), retinal vein occlusion (RVO), and diabetic macular edema (DME).[2-4] For example, the MARINA study[2] and ANCHOR study[3] showed the efficacy of ranibizumab in treating AMD.

The effect of anti-VEGF injections on intraocular pressure (IOP) has been under critical review over the past few years given the increasing use of these drugs. A short-term increase in IOP after intravitreal injections has been described in several papers.[5-9] In each of these studies, a significant elevation in IOP was found 30 min postinjection but returned to baseline levels by the first follow-up clinic visit. These studies challenged the need to perform IOP checks shortly after injection due to the transient nature of the IOP increase. This increase has been theorized to be due to an increase in volume and most often normalizes after 30 min although eyes with glaucoma may take longer to normalize. Each of these studies investigated IOP changes in patients with AMD, while very little work has been done investigating IOP changes in patients with DME.

Sustained long-term elevation in IOP has been reported with several anti-VEGF agents in a variety of diagnoses.[10-13] While many hypotheses have been generated regarding the pathophysiology behind sustained IOP elevation, a clear understanding of this phenomenon is lacking.[1,13] Proposed associations and risk factors for sustained IOP elevation include total number of injections, interval between injections, and a history of glaucoma or ocular hypertension.[13,14]

It is important to note that large clinical trials have shown that intravitreal injections do not lead to a sustained increase in IOP.[1,15-17] Significant among these studies is the *post hoc* analysis of the MARINA and ANCHOR ranibizumab trials which show that most ranibizumab-treated eyes did not experience a sustained elevation of IOP over 24 months.[16] Similarly, a large long-term study of anti-VEGF injections did not identify a history of multiple intravitreal anti-VEGF

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Manuscript received: 13.01.16; Revision accepted: 24.07.16

Cite this article as: Nariani A, Williams B, Hariprasad SM. Long-term effect of anti-vascular endothelial growth factor injections on intraocular pressure. Indian J Ophthalmol 2016;64:643-7.

injections as a significant risk factor for IOP elevation.[17] However, a recent survey of retina specialists revealed that 53% still believe that intravitreal injections may cause sustained IOP elevation.[18] Thus, debate surrounding long-term sustained elevation in IOP after intravitreal injections still persists.

Our study was designed to investigate the effects of multiple anti-VEGF injections for AMD and DME on IOP over a period of >2 years. Given the relatively high risk for developing glaucoma after RVO, our study excludes patients with this diagnosis. We also used a control group containing patients with dry AMD or diabetes mellitus without proliferative diabetic retinopathy or macular edema. This study is unique in that it tracks IOP measurements for >2 years and includes both wet AMD and DME as indications for injections. In addition, a literature review will be presented.

Methods

Study patients

This retrospective chart review was approved by the Institutional Review Board at our institution. Patients who were treated with intravitreal injections of anti-VEGF agents for wet AMD or DME before May 1, 2013, were selected for review of their medical records. Any patient with RVO was excluded as well as any patient younger than the age of 40 years. Patients in this study received between 1 and 20 intravitreal injections and IOP measurements were performed with a Tonopen (Haag-Streit, Cincinnati, Ohio, USA). The average age of patients receiving injections was 75.5 years, and the average age of control patients was 68.5 years.

IOP measurements were followed over time for as long as data were available before May 1, 2013. The range of follow-up across all patients was between 6 months and 10 years. IOP measurements were stratified according to how many months after the first injection, the measurement was taken. The following time points were used for stratification: 0–6 months, 6–12 months, 12–18 months, 18–24 months, and 24+ months after the first injection. In addition, patients were stratified by total number of injections received per eye: 1–3 injections (n = 33 for DME, n = 29 for AMD), 4–6 injections (n = 18 for DME, n = 22 for AMD), 7–9 injections (n = 6 for DME, n = 8 for AMD), and 10+ injections (n = 17 for AMD). A total of 76 eyes with AMD and 55 eyes with DME were included in the study. There were no patients in the DME cohort who received ten or more injections.

One set of controls comprised two patient types: diabetics (either without ocular complications or only with nonproliferative diabetic retinopathy) or dry AMD. Neither group had received anti-VEGF injections. This control group included 125 eyes, and its purpose was to characterize any change in IOP that may occur in these chronic conditions over time.

The second set of controls was patient who only received unilateral injections. By using the noninjected eye as a control eye and comparing IOP over time, we minimized the number of variables – both known and unknown – that affect IOP. This control group included 72 eyes, and its purpose was to detect IOP changes that could be attributed with more certainty to the intravitreal injections received.

Intravitreal injections of anti-vascular endothelial growth factor agents

Intravitreal injections of either ranibizumab (0.5 mg/0.05 mL or 0.3 mg/0.05 mL), bevacizumab (1.25 mg/0.05 mL) or aflibercept (2.0 mg/0.05 mL) were administered at our institution using an aseptic technique after the administration of topical anesthesia. Tetracaine drops and cotton-tipped applicators soaked in 4% lidocaine chloride were applied to the superotemporal conjunctival surface. Ten percent of the povidone-iodine solution was then applied to the injection site and allowed to dry for approximately 60 s before administration of the intravitreal injection. Bevacizumab was compounded by the hospital pharmacy on the site before administration. Ranibizumab and aflibercept were drawn up using a filtered needle immediately before use. A lid speculum and nonsterile gloves were used during the injection procedure. After injection, two drops of moxifloxacin hydrochloride ophthalmic solution (Vigamox, Alcon, Fort Worth, TX, USA) were applied.

The scheduled regimen for the various anti-VEGF agents varied from patient to patient depending on disease state, aggressiveness of condition, visual status of the other eye, and patient ability to return for repeated injections. The most commonly used injection protocol was treat-and-extend. Injections were typically given at 4–6-week intervals, but variability existed. In general, if optical coherence tomography confirmed resolution of intraretinal and subretinal fluid and clinical examination did not show macular subretinal fluid and/or hemorrhage (in wet AMD patients), then the treatment interval was extended by 1–2 weeks. If fluid or hemorrhage recurred, the interval was shortened.

No prophylactic therapies for IOP elevation (e.g., the use of IOP-lowering eye drops, ocular compression, or anterior chamber paracentesis) were performed before or after intravitreal injection. Central retinal artery perfusion was assessed following injection by confirming a minimum vision of hand motion. Patients with glaucoma were asked to not use their glaucoma drops in the injected eye the night of the injection but to resume the following day.

Analysis

The following variables were recorded for each patient: Age, sex, diagnosis, baseline IOP, IOP measurement before each injection, refraction, injection dates, total follow-up period, glaucoma history, total number of anti-VEGF agent injections, and anti-VEGF agent administered. As mentioned above, patients were grouped according to diagnosis (DME vs. wet AMD) and number of injections received. IOP measurements were grouped into the appropriate time periods. The univariate, one-tailed t-test was performed to test the null hypothesis that IOP does not change over time as a result of receiving intravitreal anti-VEGF injections.

Results

The first division of patients involved grouping them by disease condition: wet AMD or DME.

Fig. 1 shows the IOP measurements over time in wet AMD eyes based on number of injections received. In each subset of eyes (1–3 injections, 4–6 injections, 7–9 injections, and 10+ injections), there was no statistically significant increase in

pressure at any time point, when compared to the baseline IOP, represented as the cumulative average IOP before injections began. The *P* values obtained in this analysis are listed in Table 1.

Fig. 2 shows the IOP measurements over time in DME eyes based on number of injections received. Similar to the wet AMD patients, in each subset of eyes, there was no statistically significant increase in pressure at any time point when compared to the IOP before injections began. The *P* values obtained in this analysis are listed in Table 2.

Fig. 3 summarizes the IOP over time of patients who only received injections to one eye. The eye that did not receive injections served as the control eye. Only the subgroup undergoing 7–9 injections showed an increase in IOP, but that increase was not statistically significant. The other groups showed a decrease in IOP in the injected eye at the end of the evaluation period (May 1, 2013). The *P* values obtained in this analysis are listed in Table 3.

Finally, an analysis of 115 control eyes was performed. Patients from the control group carried a diagnosis of either diabetes mellitus (without proliferative diabetic retinopathy or macular edema) or dry AMD, and their eyes did not require anti-VEGF injections. The mean baseline IOP was 16.0, and the mean IOP after 2 years of follow-up was 15.6 ($P = 0.10$), which was not significantly different than baseline.

Discussion

The purpose of our study was to determine whether intravitreal anti-VEGF injections used for wet AMD or DME result in a sustained increase in IOP, a controversial topic within the vitreoretinal community. We used two primary methods to answer this question. The first was to analyze patients who received unilateral injections with the noninjected eye serving as the control eye and measure the difference in IOP between the injected and noninjected eyes at the end of the evaluation period. The second was to divide all injected eyes by indication (wet AMD or DME) and to measure IOP over time within different categories (number of injections received). In all cases, there was no statistically significant increase in IOP noted in our analysis. Therefore, we sought to compare our findings with those reported in the literature.

The first papers investigating IOP elevation after intravitreal anti-VEGF agents were published in late 2007 and looked at short-term effects on IOP. The previous studies had already shown that short-term IOP elevations occurred after intravitreal triamcinolone acetonide injections,[19,20] and the safety of intravitreal anti-VEGF injections became fundamentally important as their use had increased exponentially. Studies by Falkenstein *et al*.[6] and Hollands *et al*.[21] showed a transient spike in IOP that was presumably due to the increased intraocular volume after injection. However, IOP returned to baseline after the respective follow-up time (15 min[6] and 30 min[21]).

Two studies by Mojica *et al*., investigating ranibizumab[8] and bevacizumab,[7] respectively, confirmed a spike in IOP shortly after injection but continued to monitor patients after injections. Despite an increased IOP at 30 min, neither of these studies found a significant difference between pre- and post-injection IOP at future follow-up visits. They concluded that intravitreal injections of ranibizumab and bevacizumab seem to be safe from an IOP standpoint in the short-term, and that IOP monitoring may not be necessary after injections.

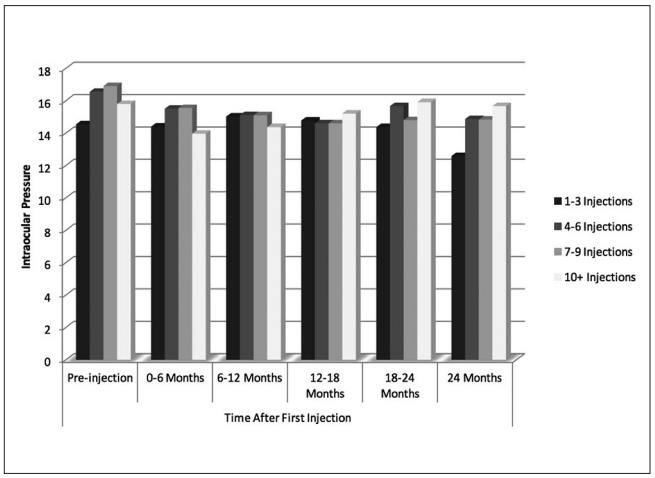

Figure 1: Intraocular pressure measurements over time in patients with wet age-related macular degeneration

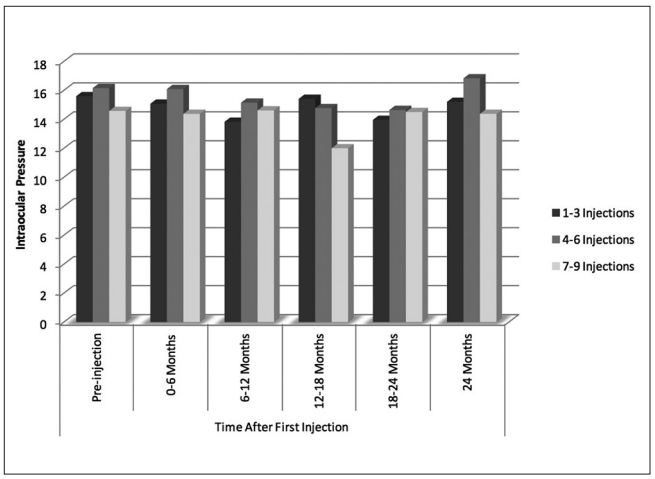

Figure 2: Intraocular pressure measurements over time in patients with diabetic macular edema

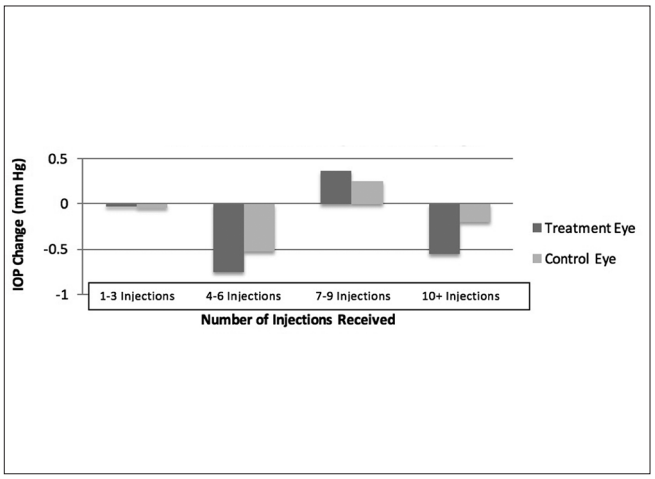

Figure 3: Unilateral injections: comparing treated eye to control eye

Table 1: Intraocular pressure over time in patients with wet age-related macular degeneration

IOP measurements over time in patients with wet AMD						
Number of injections	IOP (*P* values)					
	Baseline IOP	0-6 months	6-12 months	12-18 months	18-24 months	24+months
1-3	14.5	14.4 (0.590)	15.0 (0.234)	14.8 (0.409)	14.4 (0.696)	12.6 (0.962)
4-6	16.6	15.5 (0.955)	15.1 (0.981)	14.6 (0.904)	15.7 (0.983)	14.9 (0.963)
7-9	16.9	15.5 (0.866)	15.1 (0.892)	14.6 (0.986)	14.8 (0.970)	14.8 (0.837)
10+	15.8	14.0 (0.999)	14.4 (0.987)	15.2 (0.790)	15.9 (0.422)	15.7 (0.558)

IOP: Intraocular pressure, AMD: Age-related macular degeneration

Table 2: Intraocular pressure over time in patients with diabetic macular edema

IOP measurements over time in patients with DME						
Number of injections	IOP (*P* values)					
	Baseline IOP	0-6 months	6-12 months	12-18 months	18-24 months	24+months
1-3	15.6	15.1 (0.859)	13.8 (0.989)	15.4 (0.571)	14.0 (0.964)	15.2 (0.683)
4-6	16.2	16.1 (0.542)	15.1 (0.973)	14.8 (0.923)	14.6 (0.933)	16.8 (0.228)
7-9	14.6	14.4 (0.617)	14.6 (0.245)	12.0 (0.939)	14.5 (0.516)	14.4 (0.656)

There were no eyes with DME that underwent more than 10 injections. DME: Diabetic macular edema, IOP: Intraocular pressure

Table 3: Unilateral injections: Comparing treated eye to control eye

Unilateral injections: Comparing treated eye to control eye				
Number of injections	IOP (*P* value)			
	Baseline (treatment)	Baseline (control)	Post-injection (treatment)	Post-injection (control)
1-3	15.6	14.9	15.5 (0.47)	14.8 (0.45)
4-6	15.8	15.2	15.1 (0.22)	14.8 (0.43)
7-9	14.1	14.1	14.5 (0.34)	14.4 (0.38)
10+	14.5	14.0	13.9 (0.42)	13.8 (0.78)

IOP: Intraocular pressure

A study by Bakri *et al*. was the first to show a sustained increase in IOP after intravitreal anti-VEGF injections; they published a case series of four patients with persistent elevation of IOP after ranibizumab injections. None of the patients had any identifiable risk factor, and the elevated IOP was controlled in all eyes with medical therapy.[22] A number of case series have been published since identifying a subset of patients experiencing a sustained elevation of IOP after ranibizumab and/or bevacizumab injections.[23,24] These cases supported the need for further studies investigating the incidence of sustained elevated IOP after intravitreal anti-VEGF injections.

The recent studies have shown conflicting results concerning the existence of sustained IOP elevation after injections. Freund published three papers in support of the phenomenon of sustained IOP elevation. He described a series of 25 eyes experiencing sustained IOP elevation after ranibizumab and/or bevacizumab injections,[25] and two retrospective studies finding that a greater number of injections was associated with increased risk for IOP elevation.[12,14] One of these studies found that 7.1% of eyes experienced sustained IOP elevation,[14] while the other found this value to be 11.6% in treated eyes versus 5.3% in untreated eyes.[12]

Despite numerous studies describing a subset of patients with sustained IOP elevation, we found three studies that found no correlation between intravitreal injections and sustained IOP elevation.[17,26,27] Rates of sustained IOP elevation were found to be 3/270 injected eyes (0.5% incidence)[26] and 20/629 (3.2%)[17] in studies by Brucker and Yoon, respectively. Kim *et al*. measured average IOP at baseline and after 6, 12, 18, and 24 months and found no significant increase of IOP during the follow-up period.[27]

The recent extensive literature on the topic has produced a wide range of results. While it has been consistently shown that injections cause a short-term spike in IOP, most early papers saw this spike return to baseline and found no evidence of a sustained IOP elevation. However, a number of studies have found that a low percentage (ranging from 3.0% to 11.6%) of eyes experience a sustained increase in IOP. Some potential risk factors identified in these studies include male gender, short duration of time between injections, higher number of total injections, and history of glaucoma. Other studies have found no increased risk of sustained IOP elevation compared to noninjected eyes. It should be noted that although most studies cited by this paper specifically investigated ranibizumab and bevacizumab, our clinic began also using aflibercept in 2011. There is currently no evidence to suggest that any of these three treatments are more likely than the other to cause an increase in IOP.

It is clear that more research is needed on the topic, particularly in identifying risk factors that may put patients at increased risk for sustained IOP elevation. While many possible mechanisms have been proposed for IOP elevation after anti-VEGF injections, none have been proven. Our data are consistent with other studies that have failed to show an effect on IOP when using mean IOP as the metric to measure change over time.

Conclusions

Our data suggest that a treat-and-extend dosing regimen for anti-VEGF intravitreal injections is not a significant risk factor for an increase in IOP, regardless of how many injections the patient receives. Clinicians should use anti-VEGF agents with the confidence that long-term IOP elevations are of minimal concern and routine evaluation specifically for IOP elevation may not be necessary.

Financial support and sponsorship

Nil.

Conflicts of interest

Dr. Hariprasad is a consultant for Alcon, Allergan, Bayer, OD-OS, Clearside Biomedical, Ocular Therapeutix, Janssen, Leica, Spark, and Regeneron.

References

1. Abedi G, Adelman RA, Salim S. Incidence and management of elevated intraocular pressure with antivascular endothelial growth factor agents. Semin Ophthalmol 2013;28:126-30.
2. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, *et al.* Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419-31.
3. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, *et al.* Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432-44.
4. CATT Research Group, Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, *et al.* Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;364:1897-908.
5. Kim JE, Mantravadi AV, Hur EY, Covert DJ. Short-term intraocular pressure changes immediately after intravitreal injections of anti-vascular endothelial growth factor agents. Am J Ophthalmol 2008;146:930-4.e1.
6. Falkenstein IA, Cheng L, Freeman WR. Changes of intraocular pressure after intravitreal injection of bevacizumab (avastin). Retina 2007;27:1044-7.
7. Mazzulla DA, Hariprasad SM, Jager RD, Mieler WF. Short-term intraocular pressure trends after intravitreal injection of bevacizumab (avastin). Retin Cases Brief Rep 2008;2:234-5.
8. Mojica G, Hariprasad SM, Jager RD, Mieler WF. Short-term intraocular pressure trends following intravitreal injections of ranibizumab (Lucentis) for the treatment of wet age-related macular degeneration. Br J Ophthalmol 2008;92:584.
9. Hariprasad SM, Shah GK, Blinder KJ. Short-term intraocular pressure trends following intravitreal pegaptanib (Macugen) injection. Am J Ophthalmol 2006;141:200-1.
10. Segal O, Ferencz JR, Cohen P, Nemet AY, Nesher R. Persistent elevation of intraocular pressure following intravitreal injection of bevacizumab. Isr Med Assoc J 2013;15:352-5.
11. Mathalone N, Arodi-Golan A, Sar S, Wolfson Y, Shalem M, Lavi I, *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.
12. Hoang QV, Mendonca LS, Della Torre KE, Jung JJ, Tsuang AJ, Freund KB. Effect on intraocular pressure in patients receiving unilateral intravitreal anti-vascular endothelial growth factor injections. Ophthalmology 2012;119:321-6.
13. Singh RS, Kim JE. Ocular hypertension following intravitreal anti-vascular endothelial growth factor agents. Drugs Aging 2012;29:949-56.
14. Hoang QV, Tsuang AJ, Gelman R, Mendonca LS, Della Torre KE, Jung JJ, *et al*. Clinical predictors of sustained intraocular pressure elevation due to intravitreal antivascular endothelial growth factor therapy. Retina 2013;33:179-87.
15. Yu AL, Seidensticker F, Schaumberger M, Welge-Lussen U, Wolf A. Evaluation of intraocular pressure elevation after multiple injections of intravitreal ranibizumab. Clin Ophthalmol 2014;8:743-7.
16. Bakri SJ, Moshfeghi DM, Francom S, Rundle AC, Reshef DS, Lee PP, *et al.* Intraocular pressure in eyes receiving monthly ranibizumab in 2 pivotal age-related macular degeneration clinical trials. Ophthalmology 2014;121:1102-8.
17. Kim YJ, Sung KR, Lee KS, Joe SG, Lee JY, Kim JG, *et al.* Long-term effects of multiple intravitreal antivascular endothelial growth factor injections on intraocular pressure. Am J Ophthalmol 2014;157:1266-71.e1.
18. Yannuzzi NA, Patel SN, Bhavsar KV, Sugiguchi F, Freund KB. Predictors of sustained intraocular pressure elevation in eyes receiving intravitreal anti-vascular endothelial growth factor therapy. Am J Ophthalmol 2014;158:319-27.e2.
19. Benz MS, Albini TA, Holz ER, Lakhanpal RR, Westfall AC, Iyer MN, *et al*. Short-term course of intraocular pressure after intravitreal injection of triamcinolone acetonide. Ophthalmology 2006;113:1174-8.
20. Singh IP, Ahmad SI, Yeh D, Challa P, Herndon LW, Allingham RR, *et al*. Early rapid rise in intraocular pressure after intravitreal triamcinolone acetonide injection. Am J Ophthalmol 2004;138:286-7.
21. Hollands H, Wong J, Bruen R, Campbell RJ, Sharma S, Gale J. Short-term intraocular pressure changes after intravitreal injection of bevacizumab. Can J Ophthalmol 2007;42:807-11.
22. Bakri SJ, McCannel CA, Edwards AO, Moshfeghi DM. Persistent ocular hypertension following intravitreal ranibizumab. Graefes Arch Clin Exp Ophthalmol 2008;246:955-8.
23. Kahook MY, Kimura AE, Wong LJ, Ammar DA, Maycotte MA, Mandava N. Sustained elevation in intraocular pressure associated with intravitreal bevacizumab injections. Ophthalmic Surg Lasers Imaging 2009;40:293-5.
24. Adelman RA, Zheng Q, Mayer HR. Persistent ocular hypertension following intravitreal bevacizumab and ranibizumab injections. J Ocul Pharmacol Ther 2010;26:105-10.
25. Tseng JJ, Vance SK, Della Torre KE, Mendonca LS, Cooney MJ, Klancnik JM, *et al.* Sustained increased intraocular pressure related to intravitreal antivascular endothelial growth factor therapy for neovascular age-related macular degeneration. J Glaucoma 2012;21:241-7.
26. Wehrli SJ, Tawse K, Levin MH, Zaidi A, Pistilli M, Brucker AJ. A lack of delayed intraocular pressure elevation in patients treated with intravitreal injection of bevacizumab and ranibizumab. Retina 2012;32:1295-301.
27. Kim D, Nam WH, Kim HK, Yi K. Does intravitreal injections of bevacizumab for age-related macular degeneration affect long-term intraocular pressure? J Glaucoma 2014;23:446-8.