

Background diseases and the number of previous intravitreal aflibercept injections on immediate intraocular pressure increase and vitreous reflux rate in phakic eyes

Tetsuya Muto^{1,2,3}, Shigeki Machida¹, Shinichiro Imaizumi²

¹Department of Ophthalmology, Dokkyo Medical University Saitama Medical Center, Koshigaya 343-8555, Japan

²Imaizumi Eye Hospital, Koriyama 963-8877, Japan

³Fukushima Medical University, Fukushima 960-1295, Japan

Correspondence to: Tetsuya Muto. Department of Ophthalmology, Dokkyo Medical University Saitama Medical Center, 2-1-50 Minamikoshiyaga, Koshigaya 343-8555, Japan. ueda.castle@gmail.com

Received: 2023-03-30 Accepted: 2023-12-29

Abstract

• **AIM:** To evaluate the effect of background diseases and number of previous intravitreal aflibercept injections (IVAls) on immediate intraocular pressure (IOP) increase and vitreous reflux (VR) rate and to evaluate the correlation of both age and axial length with immediate IOP increase and VR rate.

• **METHODS:** This study included 105 patients with cystoid macular edema secondary to retinal vein occlusion, 35 patients with diabetic macular edema, 69 patients with neovascular age-related macular degeneration (nAMD), and 12 patients with myopic choroidal neovascularization, which underwent first-time IVAl. The correlation of immediate IOP increase and VR rates with the four background diseases was investigated. Moreover, the correlation of age with immediate IOP increase and VR rate as well as correlation of axial length with immediate IOP increase and VR rate were evaluated. Further, 54 patients with nAMD were treated with IVAl>10 times (multiple IVAls). Moreover, the correlation of immediate IOP increase and VR rates with first-time and multiple IVAls in nAMD was determined.

• **RESULTS:** The immediate IOP increase ($P=0.16$) and VR rates ($P=0.50$) were almost similar among the four background diseases. The immediate postinjection IOP and age, VR rate and age, immediate postinjection IOP and axial length, or VR rate and axial length were not correlated in the four background diseases. The immediate IOP increase ($P=0.66$) and VR rates ($P=0.28$) did not significantly differ between first-time and multiple IVAls in nAMD.

• **CONCLUSION:** Background diseases and number of previous IVAls have no effect on immediate IOP increase and VR rate. Further, age and axial length have no correlation on immediate IOP increase and VR rate.

• **KEYWORDS:** aflibercept; intraocular pressure; vitreous reflux; intravitreal injection

DOI:10.18240/ijo.2024.03.17

Citation: Muto T, Machida S, Imaizumi S. Background diseases and the number of previous intravitreal aflibercept injections on immediate intraocular pressure increase and vitreous reflux rate in phakic eyes. *Int J Ophthalmol* 2024;17(3):545-550

INTRODUCTION

Nowadays, intravitreal aflibercept (Eylea®; Regeneron, Tarrytown, NY, USA) injection (IVAl) is extensively used for diabetic macular edema (DME)^[1], neovascular age-related macular degeneration (nAMD)^[2], cystoid macular edema (CME) secondary to retinal vein occlusion (RVO)^[3-4], and myopic choroidal neovascularization (CNV)^[5] treatment in Japan. Intravitreal injection of anti-vascular endothelial growth factor (VEGF) antibody including aflibercept, causes an immediate increase of the intraocular pressure (IOP)^[6-8]. The immediate IOP increase is one of the risk factors for irreversible optic nerve head change^[7]. Therefore, an immediate IOP increase should be avoided as much as possible.

Vitreous reflux (VR) is frequently observed after intravitreal anti-VEGF antibody injection. VR ameliorates the immediate IOP increase^[9-11]. Uyar *et al*^[9] reported that VR rate decreased as the total number of intravitreal ranibizumab injection increased. Accordingly, the immediate IOP increased in proportion to the total number of intravitreal ranibizumab injections. These phenomena might be related to scleral thinning because repeated intravitreal anti-VEGF antibody injections caused scleral thinning around the injection sites^[12]. In contrast, Demirel *et al*^[13] reported that the total number of intravitreal ranibizumab injections was not correlated with immediate IOP increase. The correlation between the total number of IVAls and VR rate, and immediate IOP increase is

still unclear. Furthermore, the correlation between background diseases (CME secondary to RVO, DME, nAMD, and myopic CNV) and immediate IOP increase after IVAI also remains to be investigated. Therefore, the total number of IVAIs and background disease should be integrated in case of discussion of immediate IOP increase and VR after injection. Lens status has also been reported to affect immediate IOP increase or VR rate after intravitreal anti-VEGF antibody injection^[13]. Thus, we shall examine whether the background diseases and numbers of IVAIs affect VR rate and immediate IOP increase in phakic eyes.

SUBJECTS AND METHODS

Ethical Approval The study adhered to the tenets of the Declaration of Helsinki, and its protocol was approved by the Institutional Review Board at Dokkyo Medical University Saitama Medical Center (approval number 21066). Informed consent was waived due to the retrospective nature of the study.

A total of 275 eyes of 275 patients with either CME secondary to RVO, DME, nAMD, or myopic CNV who visited Dokkyo Medical University Saitama Medical Center between February 2017 and December 2022 were studied. All eyes were phakic. All patients underwent the first or multiple IVAIs (2 mg/0.05 mL) performed by one of the authors (Muto T). Overall, 54 of 275 cases of multiple IVAI had a history of >10 times injection (13.7±4.9 times) for nAMD. The IOPs were measured before and immediately after IVAIs using an ICare PRO® (Tiolat, Helsinki, Finland). The immediate postinjection IOPs were consistently measured within 1min after the IVAIs. The amount of VR was evaluated by measuring the diameter of the broadest conjunctival formation with a ruler. Patients were allocated to one of the three groups according to their VR status: group 1, patients had no VR; group 2, patients had a conjunctival bleb diameter of <3 mm; and group 3, patients had a conjunctival bleb diameter of >3 mm^[9,14]. The axial length, anterior chamber depth and lens thickness of all patients were measured using an IOLMaster 700 (Carl Zeiss Meditec AG, Jena, Germany). Patients who used anti-glaucoma eye solutions, had a history of intravitreal injection of other drugs (ranibizumab, bevacizumab, and triamcinolone acetonide) or subtenon injection of triamcinolone acetonide or vitrectomy, or had undergone cataract or glaucoma surgery were excluded from this study. Phakic patients who had a history of retinal photocoagulation were included in this study. None of the patients had used a Honan IOP reducer before intravitreal injection.

Conjunctival anesthesia was topically induced by instillation of 4% lidocaine (Xylocaine® solution 4%; Aspen Japan, Tokyo, Japan). The eyelids and ocular surface were disinfected with 0.027% iodine (PA·IODO® ophthalmic and eye washing

solution; Nitten Pharmaceutical Co., Ltd., Nagoya, Japan). In the operating room, aflibercept was injected into the superotemporal quadrant *via* the pars plana and into the vitreous cavity 3–4 mm posterior to the limbus using a 32-gauge needle (Dentronics 32 G®; Dentronics, Tokyo, Japan). Postinjection light perception was assessed. No eyes received anterior chamber paracenteses. Topical 0.5% levofloxacin solution (0.5% Cravit® ophthalmic solution; Santen Pharmaceutical, Osaka, Japan) was instilled four times daily for 3d before and after each intravitreal injection.

Statistical Analysis All data are expressed as mean±standard deviation (SD). One-way repeated-measures analysis of variance (ANOVA) was used to determine the statistical significance of patient's age, immediate preinjection IOP, immediate postinjection IOP, anterior chamber depth, lens thickness, and axial length in four background diseases. Additionally, Tukey tests were conducted after the ANOVA as post-hoc tests. Chi-square test was used to determine the statistical significance of sex, right or left eye, and VR rate. Pearson's correlation coefficient was used to evaluate the correlation of age with immediate postinjection IOP, and VR rate as well as correlation of axial length with immediate postinjection IOP, and VR rate. The unpaired *t*-test was used to determine the statistical significance of patient's age, immediate preinjection IOP, immediate postinjection IOP, anterior chamber depth, lens thickness, and axial length between patients with first-time IVAI and multiple IVAIs. These analyses were conducted using the StatMate version V for Macintosh (ATMS, Tokyo, Japan). Differences with a *P*-value <0.05 were considered statistically significant.

RESULTS

Patient characteristics in four background diseases are shown in Table 1. There were no statistically significant differences in sex (*P*=0.35) and ratio of right to left eyes (*P*=0.21) among the patients. The mean age of patients with CME secondary to RVO was older than that in patients with DME (*P*<0.01) and myopic CNV (*P*<0.01). The mean age of patients with nAMD was older than that in patients with CME secondary to RVO (*P*<0.001), DME (*P*<0.001) and myopic CNV (*P*<0.001). The mean anterior chamber depth of myopic CNV was the deepest among background diseases (*P*<0.01). Lens thickness of myopic CNV was the thinnest among background diseases (*P*<0.01). Lens thickness of CME secondary to RVO was thinner than that in patients with nAMD (*P*<0.05). Axial length of myopic CNV was the longest among background diseases (*P*<0.001) and axial length of nAMD was the shortest among background diseases (*P*<0.05).

The immediate pre- and post-injection IOP and VR rate in the four diseases are shown in Figure 1. The immediate preinjection IOPs were 16.1±3.1 mm Hg in patients with CME

Table 1 Patient characteristics in the background diseases

Parameters	RVO CME	DME	AMD	Myopic CNV	mean±SD P
Sex, M/F (n)	59/46	23/12	45/24	5/7	0.35
Mean age (y)	65.0±12.9	56.9±11.9	72.7±10.1	51.8±14.5	<0.0001
Right/left eye (n)	58/47	22/13	34/35	4/8	0.21
ACD (mm)	3.20±0.36	3.10±0.50	3.05±0.35	3.59±0.35	<0.0001
LT (mm)	4.47±0.42	4.54±0.51	4.68±0.33	4.02±0.33	<0.0001
AL (mm)	24.19±1.23	24.29±1.78	23.51±1.11	29.06±1.92	<0.0001

ACD: Anterior chamber depth; LT: Lens thickness; AL: Axial length; RVO: Retinal vein occlusion; CME: Cystoid macular edema; DME: Diabetic macular edema; AMD: Age-related macular degeneration; CNV: Choroidal neovascularization.

secondary to RVO, 16.1±3.3 mm Hg in patients with DME, 15.6±2.3 mm Hg in patients with nAMD, and 17.3±2.8 mm Hg in patients with myopic CNV (Figure 1A). The immediate postinjection IOPs were 51.7±12.3 mm Hg in patients with CME secondary to RVO, 53.0±13.7 mm Hg in patients with DME, 50.3±13.3 mm Hg in patients with nAMD, and 43.1±19.7 mm Hg in patients with myopic CNV (Figure 1B). Of 105 patients with CME secondary to RVO, 50, 28, and 27 patients were classified into groups 1, 2, and 3, respectively, according to the degree of VR. Of 35 patients with DME, 22, 5, and 8 patients of the 35 patients were classified into groups 1, 2, and 3, respectively. Of 69 patients with nAMD, 36, 21, and 12 patients were assigned to groups 1, 2, and 3, respectively. Similarly, of 12 patients with myopic CNV, 5, 4, and 3 patients were assigned to groups 1, 2, and 3, respectively (Figure 1C). There were no statistically significant among-group differences in immediate preinjection IOP ($P=0.27$), immediate postinjection IOP ($P=0.16$), and VR rate ($P=0.50$). Pearson's correlation coefficient revealed no significant correlations between immediate postinjection IOP and age (CME secondary to RVO: $P=0.23$, DME: $P=0.14$, nAMD: $P=0.68$, and myopic CNV: $P=0.48$), between VR rate and age (CME secondary to RVO: $P=0.53$, DME: $P=0.50$, nAMD: $P=0.24$, and myopic CNV: $P=0.99$), between immediate postinjection IOP and axial length (CME secondary to RVO: $P=0.074$, DME: $P=0.18$, nAMD: $P=0.44$, and myopic CNV: $P=0.11$), or between VR rate and axial length (CME secondary to RVO: $P=0.15$, DME: $P=0.42$, nAMD: $P=0.41$, and myopic CNV: $P=0.81$) in patients with the four background diseases.

The characteristics of patients with nAMD are shown in Table 2. There were no statistically significant differences in sex ($P=0.54$), mean age ($P=0.31$), ratio of right to left eyes ($P=0.78$), anterior chamber depth ($P=0.79$), lens thickness ($P=0.58$), and axial length ($P=0.074$) between the groups.

The immediate pre- and post-injection IOP and VR rate in patients with nAMD are shown in Figure 2. The immediate preinjection IOPs were 15.6±2.3 mm Hg in patients with first-time IVAI, and 15.9±2.7 in patients with multiple IVAIs (Figure 2A). The immediate postinjection IOPs were

Table 2 Patient characteristics of first-time IVAI and multiple IVAIs in phakic patients with nAMD

Parameters	First time IVAI	Multiple IVAIs	mean±SD P
Sex, M/F (n)	45/24	38/16	0.54
Mean age (y)	72.7±10.1	74.3±7.3	0.31
Right/left eye (n)	34/35	28/26	0.78
ACD (mm)	3.05±0.35	3.06±0.36	0.79
LT (mm)	4.68±0.33	4.71±0.33	0.58
AL (mm)	23.51±1.11	23.83±0.85	0.074

nAMD: Neovascular age-related macular degeneration; ACD: Anterior chamber depth; LT: Lens thickness; AL: Axial length; IVAI: Intravitreal aflibercept injection.

50.3±13.3 mm Hg in first-time IVAI, and 49.3±11.2 in multiple IVAIs (Figure 2B). Regarding VR, group 1, 2, and 3 consisted of 36, 21, and 12 patients of 69 patients with first-time IVAI, respectively. Of 54 patients with multiple IVAIs, groups 1, 2, and 3 consisted of 35, 10, and 9 patients, respectively (Figure 2C). There were no statistically significant differences between the groups in immediate preinjection IOP ($P=0.58$), immediate postinjection IOP ($P=0.66$), and VR rate ($P=0.28$) between the groups.

DISCUSSION

To the best of our knowledge, there have been no reports about the effect of background diseases on immediate IOP increase and VR rate after the first-time intravitreal injection. If the total numbers of intravitreal injections are different, deviation of immediate IOP increase and VR rates may occur. Hoang *et al*^[15] reported that sustained IOP increase may be associated with numbers of intravitreal injections. To avoid deviation, the injection number was limited for the first-time only in the current research. Several reports did not limit injected agents with one type^[16-18]. Generally, 0.1 mL of triamcinolone acetonide and 0.05 mL of anti-VEGF agents are injected to the human eye. Characteristics, such as viscosity, may be different among injected agents even though the amount is the same. There were no statistically significant among-group differences in immediate IOP increase, and VR rate after first-time IVAI. However, there were statistically significant

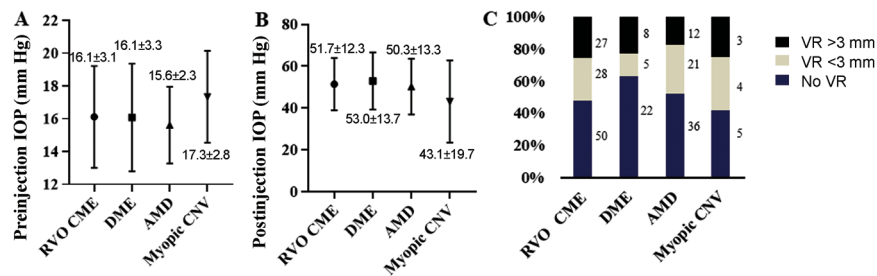


Figure 1 Preinjection IOP, postinjection IOP, and VR rate among the four background diseases A: Preinjection IOP; There were no significant differences in immediate preinjection IOP ($P=0.27$) among the four background diseases. B: Postinjection IOP; There were no significant differences in immediate postinjection IOP ($P=0.16$) among the four background diseases. C: VR rate; There were no significant differences in VR rate ($P=0.50$) among the four background diseases. IOP: Intraocular pressure; RVO: Retinal vein occlusion; VR: Vitreous reflux; CME: Cystoid macular edema; DME: Diabetic macular edema; AMD: Age-related macular edema; CNV: Choroidal neovascularization.

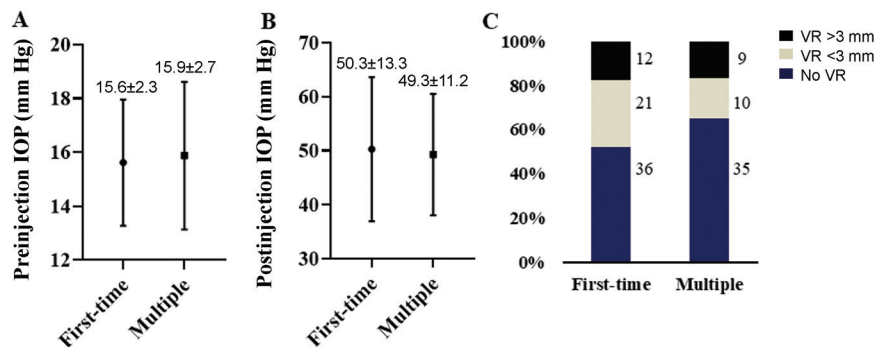


Figure 2 Preinjection IOP, postinjection IOP, and VR rate of first-time IVAI and multiple IVAI in phakic patients with nAMD A: Preinjection IOP; There were no significant differences between first-time IVAI and multiple IVAIs in immediate preinjection IOP of nAMD ($P=0.58$). B: Postinjection IOP; There were no significant differences between first-time IVAI and multiple IVAIs in immediate postinjection IOP of nAMD ($P=0.66$). C: VR rate; There were no significant differences between first-time IVAI and multiple IVAIs in VR rate of nAMD ($P=0.28$). VR: Vitreous reflux; IOP: Intraocular pressure; nAMD: Neovascular age-related macular edema; IVAI: Intravitreal aflibercept injection.

among-group differences in mean age, anterior chamber depth, lens thickness, and axial length. Uyar *et al*^[9] reported that age was not correlated with VR rate in intravitreal ranibizumab injection and our results supported their study. Cacciamani *et al*^[19] and Gismondi *et al*^[20] reported that axial length was negatively correlated with immediate IOP increase after intravitreal anti-VEGF antibody injection. However, other researchers detected no association between immediate IOP increase and axial length and our results supported their study^[19,17,21]. Although our results were different from their reports^[19-20], they used bevacizumab^[19] and ranibizumab^[20], not aflibercept. Furthermore, Gismondi *et al*^[20] did not mention about injection numbers in their report. It is difficult to simply compare the results.

Uyar *et al*^[9] reported that the number of previous intravitreal ranibizumab injection was negatively correlated with VR rate. On the other hand, Lemos *et al*^[22] reported that the number of previous intravitreal bevacizumab injections was not correlated with immediate IOP increase. The effect of the number of previous IVAIs on immediate IOP increase and VR rate was confirmed in nAMD of phakic eyes in the current study. The effect of the number of previous IVAIs does not need to be

considered in case of IVAI for nAMD of phakic eyes from our results. Although the results of Uyar *et al*'s^[9] report and ours were different, we thought the reason was character difference between ranibizumab and aflibercept. At least molecular weights were different from those of them. Although only nAMD of phakic eyes was evaluated in the current study, other background diseases in phakic eyes and pseudophakic eyes were not investigated so far. Further elucidation is warranted in the near future.

The immediate IOP increase after intravitreal injection may adversely affect the visual function^[7,23]. Lam *et al*^[18] reported that history of glaucoma surgery reduced immediate IOP increase after intravitreal anti-VEGF agent injection and recovery time of IOP to baseline was short. Furthermore, Shoeibi *et al*^[11] reported that administration of timolol, brimonidine, oral acetazolamide, and intravenous mannitol 30–60min before intravitreal bevacizumab injection did not reduce the immediate IOP increase. VR reduces immediate IOP increase^[9-11]. Chen *et al*^[24] reported that VR might be a potential cause of endophthalmitis after intravitreal injection and its visual outcome is poor^[25]. VR rates should be reduced as much as possible. Anterior chamber paracentesis can reduce

immediate IOP increase and is effective for retinal nerve fiber loss in anti-VEGF therapy^[26]. Although the onset frequency is extremely low, anterior chamber paracentesis can cause bacterial endophthalmitis and lens injuries^[27]. The accuracy of the intravitreal injection volume is a highly important factor for considering VR. Meyer *et al*^[28] determined a significant variance in the accuracy, precision and repeatability of the proposed dose for intravitreal injection. Guest *et al*^[29] reported that the IVAI volume and variability using the new prefilled syringe were significantly higher than the volume injected using the conventional BD Luer-Lok 1-mL syringe. Furthermore, Guest *et al*^[29] concluded that the design of the prefilled syringe in which aflibercept is packaged should also be reconsidered. Both new treatment methods that reduce immediate IOP increase after IVAI without VR and accurate IVAI volume measurement are warranted in current clinical practice.

ACKNOWLEDGEMENTS

Conflicts of Interest: Muto T, None; Machida S, None; Imaizumi S, None.

REFERENCES

- 1 Sugimoto M, Handa C, Hirano K, Sunaya T, Kondo M. Intravitreal aflibercept for diabetic macular edema in real-world clinical practice in Japan: 24-month outcomes. *Graefes Arch Clin Exp Ophthalmol* 2022;260(11):3489-3498.
- 2 Ohji M, Takahashi K, Okada AA, Kobayashi M, Matsuda Y, Terano Y, Investigators ALTARR. Efficacy and safety of intravitreal aflibercept treat-and-extend regimens in exudative age-related macular degeneration: 52- and 96-week findings from ALTAIR: a randomized controlled trial. *Adv Ther* 2020;37(3):1173-1187.
- 3 Shimura M, Fukumatsu M, Tsujimura J, Hirano K, Sunaya T, Investigators P. Real-world data on intravitreal aflibercept for macular edema secondary to central retinal vein occlusion: 24-month outcomes. *Clin Ophthalmol* 2022;16:579-592.
- 4 Kishishita S, Sakanishi Y, Morita S, Matsuzawa M, Usui-Ouchi A, Ebihara N. Effects of intravitreal injection of ranibizumab and aflibercept for branch retinal vein occlusion on the choroid: a retrospective study. *BMC Ophthalmol* 2022;22(1):458.
- 5 Sayanagi K, Uematsu S, Hara C, Wakabayashi T, Fukushima Y, Sato S, Ikuno Y, Nishida K. Effect of intravitreal injection of aflibercept or ranibizumab on chorioretinal atrophy in myopic choroidal neovascularization. *Graefes Arch Clin Exp Ophthalmol* 2019;257(4):749-757.
- 6 El Chehab H, Agard E, Russo A, Boujnah Y, Dot C. Intraocular pressure spikes after aflibercept intravitreal injections. *Ophthalmologica* 2016;236(1):43-47.
- 7 Gómez-Mariscal M, Puerto B, Muñoz-Negrete FJ, de Juan V, Rebolleda G. Acute and chronic optic nerve head biomechanics and intraocular pressure changes in patients receiving multiple intravitreal injections of anti-VEGF. *Graefes Arch Clin Exp Ophthalmol* 2019;257(10):2221-2231.
- 8 Dingerkus VLS, Somfai GM, Kinzi S, Orgül SI, Becker MD, Heussen FM. Incidence of severe rise in intraocular pressure after intravitreal injection of aflibercept with prefilled syringes. *Sci Rep* 2022;12(1):18136.
- 9 Uyar E, Ulas F, Sahin S, Celebi S. Major factors affecting intraocular pressure spike after intravitreal ranibizumab injection: vitreous reflux and its amount. *Eur J Ophthalmol* 2019;29(4):361-367.
- 10 Muto T, Machida S. Vitreous reflux frequency and intraocular pressure after first-time intravitreal aflibercept injections: comparison of 30- and 32-gauge needles. *Clin Ophthalmol* 2020;14:625-634.
- 11 Shoeibi N, Ghosi Z, Jafari H, Omidtabrizi A. Effect of antiglaucoma agents on short-term intraocular pressure fluctuations after intravitreal bevacizumab injections. *Int Ophthalmol* 2021;41(3):1081-1090.
- 12 Zinkernagel MS, Schorno P, Ebnetter A, Wolf S. Scleral thinning after repeated intravitreal injections of antivascular endothelial growth factor agents in the same quadrant. *Invest Ophthalmol Vis Sci* 2015;56(3):1894-1900.
- 13 Demirel S, Yanik O, Batioglu F, Ozmert E. Intraocular pressure changes related to intravitreal injections of ranibizumab: analysis of pseudophakia and glaucoma subgroup. *Int Ophthalmol* 2015;35(4):541-547.
- 14 Uyar E, Ulaş F, Alkan Y. Can vitreous reflux affect the short-term treatment response after intravitreal ranibizumab injection? *Curr Eye Res* 2021;46(2):248-254.
- 15 Hoang QV, Tsuang AJ, Gelman R, Mendonca LS, Della Torre KE, Jung JJ, Freund KB. Clinical predictors of sustained intraocular pressure elevation due to intravitreal anti-vascular endothelial growth factor therapy. *Retina* 2013;33(1):179-187.
- 16 Usman Saeed M, Batra R, Qureshi F, Clark D. Reflux of drug during intra-vitreous anti-VEGF therapies. *Semin Ophthalmol* 2011;26(6):357-360.
- 17 Hoang QV, Jung JJ, Mrejen S, Freund KB. Influence of axial length and postinjection reflux on sustained intraocular pressure elevation as a result of intravitreal anti-vascular endothelial growth factor therapy. *Retina* 2014;34(3):519-524.
- 18 Lam J, Luttrell I, Ding L, Rezaei K, Chao JR, Chee Y, Olmos De Koo LC, Wen JC. Effect of prior glaucoma surgery on intraocular pressure immediately after anti-vascular endothelial growth factor injection. *Graefes Arch Clin Exp Ophthalmol* 2019;257(11):2489-2494.
- 19 Cacciamani A, Oddone F, Parravano M, Scarinci F, Di Nicola M, Lofoco G. Intravitreal injection of bevacizumab: changes in intraocular pressure related to ocular axial length. *Jpn J Ophthalmol* 2013;57(1):63-67.
- 20 Gismondi M, Salati C, Salvetat ML, Zeppieri M, Brusini P. Short-term effect of intravitreal injection of Ranibizumab (Lucentis) on intraocular pressure. *J Glaucoma* 2009;18(9):658-661.
- 21 Höhn F, Mirshahi A. Impact of injection techniques on intraocular pressure (IOP) increase after intravitreal ranibizumab application. *Graefes Arch Clin Exp Ophthalmol* 2010;248(10):1371-1375.
- 22 Lemos V, Cabugueira A, Noronha M, Abegão Pinto L, Reina M, Branco J, Gomes T. Intraocular pressure in eyes receiving intravitreal

- antivascular endothelial growth factor injections. *Ophthalmologica* 2015;233(3-4):162-168.
- 23 Rebolleda G, Puerto B, de Juan V, Gómez-Mariscal M, Muñoz-Negrete FJ, Casado A. Optic nerve head biomechanics and IOP changes before and after the injection of aflibercept for neovascular age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2016;57(13):5688-5695.
- 24 Chen SDM, Mohammed Q, Bowling B, Patel CK. Vitreous wick syndrome—a potential cause of endophthalmitis after intravitreal injection of triamcinolone through the pars plana. *Am J Ophthalmol* 2004;137(6):1159-1160; author reply 1160-1161.
- 25 Dar N, Pillar S, Friehmann A, Belkin A, Ofir S. Endophthalmitis after intravitreal injections versus cataract surgery: a 15-year cohort. *Int Ophthalmol* 2020;40(1):73-79.
- 26 Enders P, Sitniska V, Altay L, Schaub F, Muether PS, Fauser S. Retinal nerve fiber loss in anti-VEGF therapy for age-related macular degeneration can be decreased by anterior chamber paracentesis. *Ophthalmologica* 2017;237(2):111-118.
- 27 Saxena S, Lai TY, Koizumi H, Farah ME, Ferrara D, Pelayes D, Sato T, Meyer CH, Murray T, International Pharmacokinetic Collaboration. Anterior chamber paracentesis during intravitreal injections in observational trials: effectiveness and safety and effects. *Int J Retina Vitreous* 2019;5:8.
- 28 Meyer CH, Liu Z, Brinkmann C, Rodrigues EB, Helb HM. Accuracy, precision and repeatability in preparing the intravitreal dose with a 1.0-cc syringe. *Acta Ophthalmol* 2012;90(2):e165-e166.
- 29 Guest JM, Malbin B, Abrams G, Parendo A, Das S, Okeagu C, Ross BX, Kumar A, Lin XH. Accuracy of intravitreal injection volume for aflibercept pre-filled syringe and BD Luer-Lok one-milliliter syringe. *Int J Retina Vitreous* 2022;8(1):27.