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Effect of Prefilled vs Vial-Drawn Syringes on Sustained Increases in Intraocular Pressure in Patients Treated With Aflibercept

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Abstract

Purpose: To evaluate the effect of syringe type on developing sustained intraocular pressure (IOP) increases. **Methods:** This retrospective cohort study included patients in a single academic center receiving antivascular endothelial growth factor (anti-VEGF) injections from 2012 to 2022 for various indications. Patients were grouped by anti-VEGF treatment of either vial-drawn or prefilled syringe delivery. Trends in IOP were recorded for 1 year after treatment began. Development of sustained IOP increase, ocular hypertension, and glaucoma was recorded. Sustained IOP increase was defined as ≥5 mm Hg above baseline for at least 4 weeks. **Results**: Of 257 total patients, 6 (2.3%) developed sustained IOP increases throughout the study's duration. No significant differences were noted with respect to prefilled versus vial-drawn syringe status on the development of sustained IOP increases or incident glaucoma (IOP: 1.8% vs 2.7%, respectively, $P = .65$; glaucoma: 0.0% vs 2.0%, respectively, $P = .14$). Patients treated with prefilled syringes were significantly less likely to develop ocular hypertension (2.8% vs 8.8%, $P < .05$). **Conclusions:** This study found that aflibercept intravitreal injection with prefilled syringes was not associated with a significant increase in IOP-related adverse effects when compared with those treated with vial-drawn syringes.

Keywords

intravitreal injection, prefilled syringe, sustained intraocular pressure increase

Introduction

Diabetic retinopathy (DR), age-related macular degeneration (AMD), and retinal vein occlusion (RVO) are leading causes of ocular morbidity worldwide.[1] Intravitreal antivascular endothelial growth factor (anti-VEGF) inhibitor injections are the standard of care for managing edema and neovascularization associated with late stages of these conditions.[2–4] The 3 commonly used anti-VEGF injections bevacizumab, ranibizumab, and aflibercept are well-studied and have been shown to decrease neovascularization while improving visual outcomes in retinal vascular diseases.[2–4]

Overall, intravitreal injections (IVIs) for delivery of anti-VEGF demonstrate a minimal risk profile.[5] An increase in intraocular pressure (IOP) is a known adverse effect that may occur immediately after injection due to acute volumetric expansion of the eye, but the increased IOP often subsides within 1 to 2 hours.[6,7] However, Good et al[8] in 2011 reported that IVI with bevacizumab or ranibizumab may be associated with chronic IOP elevation in patients with neovascular AMD. Bakri et al[9] in 2014 examined IOP changes in the MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) and ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD) studies, finding significantly higher rates of sustained IOP increases in patients treated with ranibizumab compared with sham controls. Further post hoc analysis of randomized controlled trials showed treatment with anti-VEGF to significantly increase the risk for sustained IOP increases compared with those treated with panretinal photocoagulation or laser.[10] Contradicting this notion, Kähkönen et al[11] recently investigated patients treated

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with bevacizumab and aflibercept and found no significant increase in sustained IOP changes compared with untreated fellow eyes. More studies are needed to draw further conclusions.

Multiple variables may be related to sustained increases in IOP, such as the type of injection agent, the frequency of injection, and the underlying indication for injection.[10] Further, prefilled injection syringes may be associated with higher rates of sustained IOP increases.[12] Although sustained IOP increases post injection with anti-VEGF have been reported, the frequency that this adverse effect occurs with aflibercept as well as stratification by syringe type (prefilled vs vial drawn) remains to be elucidated. This study aims to assess in a large cohort of patients treated with aflibercept the effect of syringe type on the likelihood of developing sustained IOP increases.

Methods

The study protocol was approved by the institutional review board. The electronic medical records were queried for all patients aged 18 years or older being treated with aflibercept for management of ocular disease between January 1, 2012, and May 30, 2022, at Cleveland Clinic Cole Eye Institute, and 668 patients were identified. Of this cohort, treatment-naive patients seen clinically for AMD, RVO, or DR whose medical record included follow-up IOP data were included. One eye per patient was included at random. Exclusion criteria included ocular surgery 30 days before initial injection or anytime throughout the study period, history of ocular or cranial trauma, and prior anti-VEGF treatment. After these cutoffs, 257 patients met the criteria.

Patients were stratified into either vial-drawn or prefilled syringe treatment cohorts based on the date of first intravitreal injection. In July 2020, Cole Eye Institute switched from using vial-drawn intravitreal injection to prefilled syringe delivery. Therefore, patients treated before 2020 were designated into the vial-drawn cohort, while those who began treatment after July 2020 were allocated to the prefilled syringe cohort. To reduce confounding, patients whose study period spanned July 2020 were not included as they may have received both vial and prefilled syringe treatment.

Baseline clinical information was collected to include sex, age, race, and smoking history. Baseline IOP was determined by averaging IOP measurements taken during the most recent visit before injection and on the date of initial injection. Patients were then classified by continuous treatment with either vial-drawn or prefilled syringe throughout the 12-month study period. Additional collected variables tracked over the 12-month study period included trends in IOP at follow-up visits, development of sustained IOP increase, number of subsequent injections given, development of ocular hypertension (OHTN), and clinical diagnosis of glaucoma. These incident diagnoses were only counted as positive if found within the 12-month study period. As in prior studies, sustained IOP increase was defined as ≥5mm Hg from baseline for at least 4 weeks.[10] The incidence of OHTN was defined as a pressure increase of ≥22 mm Hg at any time throughout the study duration.[13]

Data were reported as frequency and percentages or means and standard deviations. Independent-sample *t* tests and analysis of variance testing were used to compare mean differences between groups with respect to continuous variables. Chi-square testing was used to analyze categorical variables. Statistical analysis was performed using JMP statistical software (version 16, JMP Statistical Discovery), and *P* values less than 0.05 were considered statistically significant.

Results

Demographics

A total of 257 aflibercept-treated eyes were included in this study. The 109 eyes in the prefilled syringe cohort belonged to patients who were a mean 79.7 ± 9.6 years old, 73.4% female, and 86.2% White. The 148 eyes in the vial-drawn cohort were on average 82.8 ± 11.9 years old, 47.3% female, and 88.5% White. Complete demographic information can be found in Table 1.

Frequency of Sustained IOP Increases

Of the 257 eyes examined in the cohort, sustained IOP increases were noted in 6 cases, for a total frequency of 2.3%. Of these 6 cases, 4 were noted in the vial-drawn cohort (2.7%) while 2 were noted in the prefilled cohort (1.8%). No significant difference was seen in the frequency of sustained IOP increases between these 2 groups (Table 2). With respect to characteristics of the sustained IOP increases, no trends were noted with respect to treatment indication, number of injections in the study period, age, or sex (Table 3).

Frequency of Ocular Hypertension

OHTN was noted in 16 of the 257 eyes examined, for a combined frequency of 6.2%. Patients being treated for DR (8.1%) and RVO (11.4%) developed OHTN at a higher rate than those being treated for AMD (4.4%), but no statistical significance was seen. The vial-drawn cohort (8.8%) had a significantly higher frequency of OHTN than the prefilled cohort (2.8%) ($P = .048$) (Table 4).

Development of Glaucoma

Of the 257 eyes included in the study, 3 (1.2%) developed new-onset glaucoma. All of these cases were noted in the vial cohort (2.0%) compared with the prefilled syringe cohort (0%) ($P = .14$) (Table 5). No trends were seen in this case with respect to age, disease status, or number of cumulative injections over the treatment period (Table 6).

Conclusions

Sustained IOP increase was noted in 6 of 257 eyes (2.3%), which is lower than what has been reported in previous literature.[8,9,14–17] These current findings align with those of Wehrli

Table 1. Cohort Demographics (N = 257).

Demographic	Vial Drawn (n = 148)	Prefilled Syringe (n= 109)	*P* Value
Mean age, (y) ± SD	82.8 ± 11.9	79.7 ± 9.6	.03[b]
Sex, n (%)			<.001[b]
Female	70 (47.3)	80 (73.4)	
Male	78 (52.7)	29 (26.6)	
Race, n (%)			.75
Black	11 (7.3)	11 (10.1)	
White	131 (88.5)	94 (86.2)	
Other[a]	6 (4.0)	4 (3.7)	
Smoking status, n (%)			.077
Current	3 (2.0)	7 (6.4)	
Former	74 (50.0)	43 (39.5)	
Never	71 (48.0)	59 (54.1)	
Eye laterality, n (%)			.91
Right	79 (53.4)	59 (54.1)	
Left	69 (46.6)	50 (45.9)	

[a]Other race includes Asian, Pacific Islander, American Indian, or unreported.
[b]Statistically significant difference ($P < .05$).

Table 2. Incidence of Sustained IOP Increases in Study Cohorts.

	Cohorts, n (%)			
Sustained Elevated IOP	Vial Drawn (n = 148)	Prefilled Syringe (n = 109)	Total (N = 257)	*P* Value
Yes	4 (2.7)	2 (1.8)	6 (2.3)	.65
No	144 (97.3)	107 (98.2)	251 (97.7)	

Abbreviation: IOP, intraocular pressure.

Table 3. Characteristics of Study Patients With Sustained Elevated IOP (n = 6).

Case No.	Age (Y)	Sex	Laterality	PFS or Vial	Indication for IVI	Injections in Year (n)	Time From First Injection to IOP Increase (Days)
1	73.9	Male	OD	Vial	DR	3	204
2	67.5	Male	OD	Vial	DR	4	168
3	90.6	Male	OS	Vial	AMD	11	29
4	77.3	Female	OS	PFS	AMD	11	102
5	56.1	Male	OD	Vial	DR	5	147
6	99.3	Female	OS	PFS	RVO	3	112

Abbreviations: AMD, age-related macular degeneration; DR, diabetic retinopathy; IOP, intraocular pressure; IVI, intravitreal injection; OD, right eye; OS, left eye; PFS, prefilled syringe; RVO, retinal vein occlusion.

et al[18] and a recent study by Kähkönen et al[11] that showed low frequency of sustained IOP increases after initiation of VEGF.

In addition to reporting on IOP elevation, the present study examined syringe type in a large cohort of treatment-naive patients initiating VEGF treatment with aflibercept. Prefilled syringes for IVI have recently been called into question since the release of a 2021 report from the European Medical Agency suggesting an increased risk for elevated IOP with prefilled syringes.[12] Siedlecki et al[19] examined IOP spikes in patients treated with prefilled syringes versus vials and found a 5-fold increase in the prefilled syringe cohort compared with vial draw. Siedlecki et al[19] defined IOP spikes as the loss of perception of hand movement for 30 seconds after an injection. The patients were not followed longitudinally for the development of sustained increases in IOP, leaving the clinically relevant longitudinal effects of these IOP spikes unknown.

These differences in methodologies may account for the low frequency of sustained IOP increases in the present study.

Table 4. Characteristics of Patients With and Without OHTN.

Factor	Patients, n (%)		*P* Value
	With OHTN (n = 16)	Without OHTN (n = 241)	
No. of injections/y			.195
≤3	3 (3.2)	91 (96.8)	
4-7	5 (10.9)	41 (89.1)	
≥8	8 (6.8)	109 (93.2)	
Indication for injection			.232
AMD	7 (4.4)	153 (95.4)	
DR	5 (8.1)	37 (91.9)	
RVO	4 (11.4)	31 (88.6)	
PFS vs vial drawn			<.05[a]
Vial drawn	13 (8.8)	135 (91.2)	
PFS	3 (2.8)	106 (97.2)	

Abbreviations: AMD, age-related macular degeneration; DR, diabetic retinopathy; OHTN, ocular hypertension; PFS, prefilled syringe; RVO, retinal vein occlusion.
[a]Statistically significant difference ($P < .05$).

Table 5. Incidence of Glaucoma Development in Study Cohorts During Study Period (1 Year).

New Glaucoma Diagnosis	Cohorts, n (%)			*P* Value
	Vial Drawn (n = 148)	Prefilled Syringe (n = 109)	Total (N = 257)	
Yes	3 (2.0)	0	3 (1.2)	.14
No	145 (98.0)	109 (100)	254 (98.8)	

Table 6. Characteristics of Study Patients With Glaucoma.

Case No.	Age (Y)	Sex	Laterality	PFS or Vial	Indication for IVI	Injections in Year (n)
1	98.6	Female	OD	Vial	AMD	3
2	56.1	Male	OD	Vial	DR	5
3	92.7	Male	OD	Vial	AMD	8

Abbreviations: AMD, age-related macular degeneration; DR, diabetic retinopathy; IVI, intravitreal injection; OD, right eye; PFS, prefilled syringe.

Furthermore it is possible the immediate spikes Siedlecki et al[19] defined may be transient and not clinically detrimental to long-term care. El Chehab et al[20] support this hypothesis, finding that IVIs lead to transient increases in IOP that return to baseline within 45 minutes after injection.

Clinician technique while performing IVI may also be associated with transient pressure spikes post injection. Dingerkus et al[21] examined the effect of injection pressure on the amount of suspension delivered and found significant increases in emptying volume when syringes were forcefully emptied compared with normal emptying. Guest et al[22] and Goldberg[23] found increased variability in the amount of suspension delivered in prefilled syringes of aflibercept, hypothesizing this variation may lead to adverse IOP effects with the use of prefilled syringes. However, the present study suggests prefilled syringes do not contribute to sustained IOP increases, development of OHTN, or glaucoma.

While transient increases in IOP are a known consequence of IVI, the associations of sustained increases in IOP post IVI are still unclear. Pooled analyses of IVI and sustained IOP increase have shown a prevalence interval of 2% to 11%.[10] The prevalence in the present study is on the lower end of the spectrum of these estimates, with a total cohort prevalence of 1.9%. However, this may be due to small cohorts leaving this study statistically underpowered. To detect significant differences in the prevalence of sustained IOP increases across groups, a sample size of more than 1000 patients would be necessary, assuming a 2% difference in incidence between arms, a power of 0.8, and an alpha level of 0.05. To date, most reports investigating sustained IOP increases after IVI at single centers have comprised fewer than 300 patients. Pooling larger cohorts comparing syringe types will be necessary in future work.

The type of injection agent may also be a notable variable when examining sustained IOP increases. The associations of

aflibercept with sustained IOP increases are far less reported than those with ranibizumab and bevacizumab. Freund et al[24] reported a lower incidence of sustained IOP increase in patients treated with aflibercept compared with ranibizumab. However, Kähkönen et al[11] did not find such associations when comparing aflibercept with ranibizumab, possibly due to a small cohort size. It is hypothesized these associations may also be due to the molecular structure of anti-VEGF agents in addition to the increased volumetric expansion in the eye. Studies have suggested that bevacizumab may confer an increased risk for interfering with drainage through the trabecular meshwork due to its large molecular weight of 148 kDa compared with ranibizumab (48 kDa) and aflibercept (115 kDa).[25,26] Supporting this notion, our study found low rates of sustained elevated IOP with aflibercept but lacked an appropriate ranibizumab and bevacizumab comparator arm because ranibizumab syringe status was not able to be ascertained from the electronic medical record at the single tertiary care center in this study (Table 2).

Strengths of this study reside in the novelty of data reported with respect to syringe status, the treatment-naive cohort, examination of patients treated with aflibercept, and the study's applicability to patients in routine clinical practice. As the association of IVIs with increases in IOP remains unclear, this study adds to the current literature that suggests sustained increases in IOP may be less frequent than previously thought and will help guide future large-scale studies.

This study shares limitations common to retrospective review, such as the loss to follow-up, which limited conclusions that can be drawn at progressive timepoints. The necessarily strict exclusion criteria, lack of follow-up, and single-institution data pool placed constraints on this cohort, likely leading to an underpowered analysis of a rare adverse event. Additionally, single point in time measurements used as outcomes can increase the likelihood of error, especially in low-incidence events. While trends were noted in many of the analyses, statistical significance was not achieved. Future large-scale pooled studies will be needed to assess the true impact of IVI on sustained IOP increases compared with control cohorts.

In conclusion, this study is the first of our knowledge to examine sustained IOP increases among syringe type in a large cohort of patients given aflibercept. Patients were found to have lower but not statistically significant rates of sustained IOP increases and glaucoma development in the prefilled syringe cohort relative to the vial-drawn cohort. This study adds to the existing literature challenging the associations between IVI and ocular pressure abnormalities. Higher powered cohorts are essential to further solidify the associations seen in this study.

Ethical Approval

This study was approved by the Cleveland Clinic Institutional Review Board.

Statement of Informed Consent

Informed consent was not obtained from patients as no patient level images or identifying information was utilized in this study. Study-related procedures were performed in accordance with good clinical practice (International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use E6), applicable US Food and Drug Adminstration regulations, the Health Insurance Portability and Accountability Act, and the Declaration of Helsinki.

Declaration of Conflicting Interests

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