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Transient Vision Loss Associated with Prefilled Aflibercept Syringes

A Case Series and Analysis of Injection Force

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Purpose: To describe cases of significant vision loss after intravitreal aflibercept administration using prefilled syringes (PFS) and to study the relationships among syringe design, injection speed, and injection force.

Design: Retrospective case series and experimental study.

Participants: Twelve patients who received intravitreal aflibercept via PFS.

Methods: All retina specialists (n = 13) at Oregon Health & Science University and the Veterans Affairs Portland Medical Center were queried in December 2020 to report episodes of significant vision loss after aflibercept PFS use. Chart review was completed for all affected patients. Using a commercially available force measuring system, injection force was measured for aflibercept PFS, ranibizumab PFS, and a tuberculin syringe at various injection speeds.

Main Outcome Measures: Number of significant vision loss episodes after aflibercept PFS use and average injection force (Newtons) at various injection speeds across different syringes.

Results: Ten specialists (76.9%) reported a perceived increase in vision loss after injection with aflibercept PFS. Sixteen events of light perception or worse vision were reported immediate after aflibercept PFS use. Chart review was available for 12 of these events. The indication for aflibercept was exudative age-related macular degeneration (n = 8), diabetic macular edema (n = 3), and central serous chorioretinopathy (n = 1). The median age of affected patients was 71 years (range, 49–94 years). Two patients were being treated for glaucoma (n = 1) or ocular hypertension (n = 1); 1 patient was a glaucoma suspect. Anterior chamber paracentesis was performed in 4 patients to normalize intraocular pressure (IOP) promptly. Laboratory experiments demonstrated that higher injection speeds were associated with higher injection forces for all syringe types. Injection forces were consistently greater with aflibercept PFS than with the ranibizumab PFS or tuberculin syringe ($P < 0.0001$).

Conclusions: Retina specialists at our institutions have noted numerous cases of severe transient vision loss with aflibercept PFS use. The average injection force may be greater with the aflibercept PFS when compared with other intravitreal anti–vascular endothelial growth factor (VEGF) options. Additional clinical studies are needed to understand better how syringe design and fluid dynamics may contribute to vision loss after injection. *Ophthalmology Science 2022;2:100115 Published by Elsevier on behalf of the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Aflibercept (Eylea; Regeneron Pharmaceuticals, Inc) is an anti–vascular endothelial growth factor (VEGF) agent that was approved by the United States Food and Drug Administration in 2011 and currently is used in the management of exudative age-related macular degeneration (AMD), macular edema occurring after retinal vein occlusion, diabetic macular edema, and diabetic retinopathy.[1] More recently, in 2019, the Food and Drug Administration approved the use of aflibercept prefilled syringes (PFS) for intravitreal use.[2] Prefilled syringes have several advantages over traditional vial intravitreal preparations, including reduced overall preparation and injection time, improved precision in the volume and resultant dose administered, and increased ease of use.[3] These measures should translate to improved patient safety outcomes and overall improved clinic workflow.[4]

Intravitreal injections can be associated with potential vision-threatening complications, including endophthalmitis, retinal detachment, intraocular pressure (IOP) elevation, and central retinal artery occlusion.[5] Retina specialists at our institutions have noted an increased incidence of severe transient vision loss with the adoption of aflibercept PFS when compared with traditional aflibercept vial preparations. Similar observations have been made by others. Earlier this year, a higher than expected proportion of cases of elevated IOP after aflibercept PFS was noted by the European Medicines Agency.[6] A recent correspondence to The Royal College

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of Ophthalmologists reported a small case series 4 patients whose 5 eyes also demonstrated transient central retinal artery occlusions after injection with an aflibercept PFS.[7]

Although prior reports suggest that user error via plunger misalignment is the primary reason for the adverse events after aflibercept PFS use, this explanation alone may be incomplete.[6–8] Our group hypothesized that syringe design also may play a critical role in these outcomes and that the wider syringe diameter of the aflibercept PFS may elicit larger injection forces. Further investigation is warranted. To this end, we sought to describe cases of significant vision loss and IOP spikes after intravitreal aflibercept PFS and to elucidate further how factors related to syringe design may contribute to these outcomes.

Methods

Patient Data Collection

This study followed the tenets of the Declaration of Helsinki. Informed consent was not necessary because of the retrospective nature of this study. Institutional review board approval was obtained at Oregon Health & Science University and the Veteran Affairs Portland Health Care System (protocol no. 5031) before initiation of this study. All retina specialists from both institutions (n = 13) were queried in December 2020 to determine their experience with aflibercept PFS, which were made available at both institutions in February 2020. Specialists were asked to report any episodes of significant vision loss after injection (i.e., vision worse than counting fingers), definite or presumed intraocular pressure spike (i.e., lack of optic nerve perfusion, error reading using Tono-Pen), or both in at least 1 eye immediately after administration of aflibercept using a PFS. The medical records of all patients who experienced these complications were reviewed for patient age, gender, laterality of procedure, indication for anti-VEGF use, history of prior anti-VEGF injections, lens status (e.g., phakic vs. pseudophakic), prior pars plana vitrectomy, history of glaucoma or ocular hypertension, use of IOP-lowering drops, Snellen visual acuity (VA) before the procedure, IOP before the procedure, VA immediately after injection, anterior chamber tap after the procedure, and VA at the next follow-up visit. Axial length was recorded, if available, in pseudophakic patients, and refraction (converted to spherical equivalent) was obtained for patients with phakia. In patients receiving aflibercept for diabetic retinopathy, the chart was reviewed to determine if active neovascularization was present.

Measuring Injection Force

Injection force was measured using an Instron 3345 universal testing system (Instron). A syringe-holding unit was mounted for lateral and vertical positioning to make sure that the force always was applied to the center of the plunger. The unit was modified further with an XYZ syringe positioner as well as a telecentric lens optical system positioned orthogonally to measure the fill level of the syringe precisely (Fig 1). Our optical system consisted of a 660-nm illumination source (Advanced Illumination RL1424 Small Aimed Bright Field source with a CS410 Advanced Illumination constant current source computer-controlled power supply), telecentric lens (Edmund Optics 0.16X Silver TL Telecentric lens), and a c-mounted USB 3.0 CMOS camera (Basler Ace acA2040 90-μm progressive scan CMOS sensor, 4-megapixel resolution). The optical system was mounted on the plate that moved vertically to follow the position of the syringe plunger

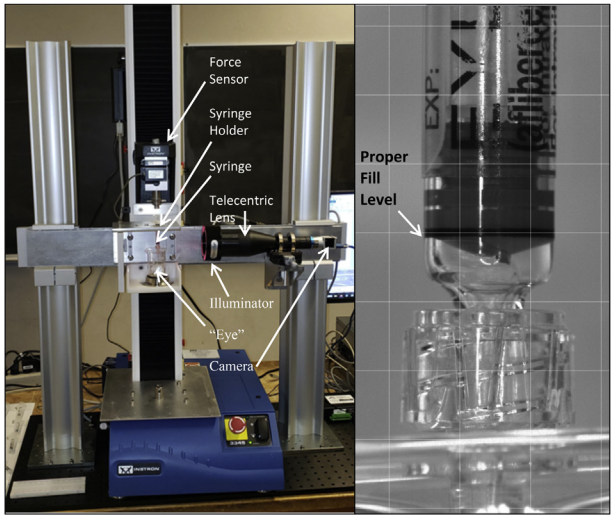

Figure 1. A, Photograph showing the syringe force measuring system with attached telecentric lens system. B, Telecentric photograph showing an aflibercept prefilled syringe and the proper fill level for the plunger tip location.

positioning and alignment. Syringe position was monitored using Basler imaging software (pylon viewer 64-bit) with a rate of 10 frames per second with a 2048 × 2048 pixel image.

Three syringe types were tested in this study: the glass syringe prefilled with aflibercept, the glass syringe prefilled with ranibizumab (Lucentis; Genentech, Inc), and the 1-ml tuberculin plastic syringe (Monoject; Cardinal Health). Similar to prior literature, the syringe barrel inner diameter was measured to be 6.26 mm for the aflibercept glass syringe, 4.63 mm for the ranibizumab glass syringe, and 4.76 mm for the tuberculin plastic syringe in this study.[7] Each syringe was connected to a 30-gauge needle (PrecisionGlide, BD), which has an inner diameter of 152 μm, and was filled with 0.05 ml of balanced salt solution (Alcon Laboratories, Inc), which has a pH of 7.5 and an osmolality of 300 mOsm/kg.[9] Assuming that the fluid is incompressible, we also can assume that the fluid density does not change in either the syringe barrel or the 30-gauge needle. Because the injection velocities, V_1, for the injection are set as constant by the system (either 0.665 mm/second, 1.33 mm/second, 2.66 mm/second, or 3.9 mm/second), one knows the ejection velocity, V_2, can be calculated using the continuity equation

$$V_2 = V_1 \frac{A_{\text{plunger}}}{A_{\text{needle}}},$$

where A_{plunger} is the plunger area in square millimeters and the A_{needle} is the needle flow cross-sectional area in square millimeters. The velocity (V_2) values for the 0.67-mm/second, 1.33-mm/second, 2.66-mm/second, and 3.90-mm/second injection speeds were determined to be 1130 mm/second, 2260 mm/second, 4510 mm/second, and 6610 mm/second, respectively.

Intravitreal injections were simulated by injecting into a hydrophilic gel polymer ball (models GB-760 and GB-710; Education Innovations, Inc.). Given that human eyes measure an average of 23.8 mm in diameter, hydrophilic polymers were prefilled with water to a size of 24 ± 3 mm (Fig 2).[10] Although the entire chemical composition for this polymer is not publicly available, sodium acrylate (sodium prop-2-enoate) is a common material for these types of hydrophilic polymers with a density of 1.22 g/cm^3, which is comparable to the density of the human eye (1.02 ± 0.03 g/cm^3).[11,12]

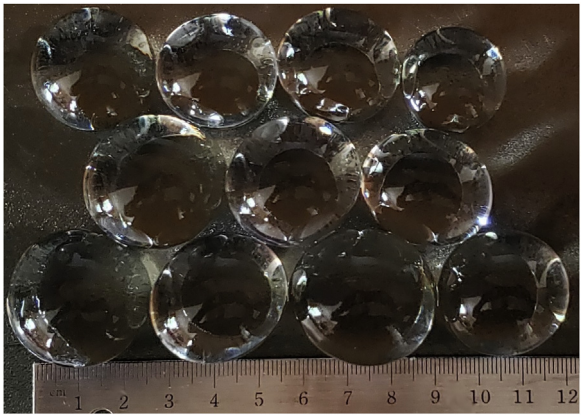

Figure 2. Photograph showing hydrophilic water gels.

The procedure used to measure injection force with the 3 syringes (aflibercept PFS, ranibizumab PFS, and tuberculin syringe) was as follows:

1. The syringe first was attached to a 30-gauge needle and filled with slightly more than 0.05 ml of balanced salt solution. All air bubbles were removed.
2. The syringe then was placed into the metal holding unit for the appropriate syringe type and size holder, and any excess fluid was wasted. The optical detection system was focused onto the syringe to verify the proper fill level (Fig 1).
3. The needle was lowered into the hydrophilic polymer.
4. The force sensor was placed above the syringe plunger.
5. The test method in the software was run at each velocity (0.67 mm/second, 1.33 mm/second, 2.67 mm/second, and 3.90 mm/second). The end-of-test detection was set to a force level of 50 Newtons or more, a value that should not be seen with normal intravitreal injection use. Data points were obtained at 20-ms intervals.
6. As soon as a level of 50 Newtons was reached, the trial run was deemed complete, and the above steps were repeated for the next trial run. To obtain a fair representation of the injection force, 10 trial runs were performed using each syringe type at each velocity.
7. On average, recalibration of the force sensor was performed after 5 trial runs, and rebalancing (zeroing) occurred before each run.

Statistical Analysis

Statistical analyses were performed using Prism software version 9 (GraphPad). Differences in injection force were analyzed first by measuring the area under the receiver operating characteristic curve, using the trapezoidal rule, from the starting point to the 2-mm syringe extension for each syringe type at the 4 different velocities. An end point of 2 mm was selected for 2 reasons: (1) it sufficiently captured the break loose force and syringe glide force and (2) force measurements beyond this point were more likely to reflect the force needed to deform the syringe plunger tip as it hit the syringe bulb (up to 50 Newtons). The D'Agostino-Pearson test was used to assess normality (using $P < 0.05$ as a cutoff). The Kruskal–Wallis 1-way analysis of variance test with Dunn's post hoc analysis was used for comparison of 3 or more groups. Violin plots represented 25th to 75th percentiles, with vertical bars providing range and horizontal bars representing median values. Statistical significance was defined as $P < 0.05$ for all analyses.

Results

Thirteen retina specialists were queried. Ten specialists (76.9%) reported observing at least 1 episode of severe transient vision loss after aflibercept PFS use, whereas 3 specialists observed no cases of vision loss. Sixteen confirmed events of no light perception or light perception vision immediately after aflibercept PFS use were reported. Three physicians reported observing more than 1 event. All retina specialists used a 30-gauge needle for intravitreal injection. Chart review was available for 12 of these 16 events (Table 1). The median age of the affected patients was 71 years (range, 49–94 years). Four patients (33%) were women. The indication for aflibercept was exudative AMD (n = 8), diabetic macular edema (n = 3), or choroidal neovascularization secondary to central serous chorioretinopathy (n = 1). No patients with diabetes had active neovascularization. Only 1 patient had a prior history of pars plana vitrectomy for nonclearing vitreous hemorrhage. Two patients were being treated for glaucoma (n = 1) or ocular hypertension (n = 1); 1 patient had suspected glaucoma and was not receiving IOP-lowering treatment. Four patients underwent an anterior chamber paracentesis after the episode of severe transient vision loss, whereas the vision of the remaining patients improved without any procedural intervention. Visual acuities were stable or improved for all patients at the subsequent clinic visit when compared with the VA before the procedure. Three patients requested switching back to traditional self-filled aflibercept vial preparations because they experienced significant injection-related anxiety as a result of the transient severe vision loss they experienced with aflibercept PFS. Several patients' cases are described further detail below. All patients are summarized in Table 1.

Case Reports

Patient 1. A 72-year-old man with phakia underwent intravitreal injection using an aflibercept PFS in the right eye for exudative AMD. Before the procedure, VA was 20/50 with IOP of 12 mmHg. Immediately after injection, vision was recorded as no light perception for 1 minute before seeing hand movements. No intervention was needed. At follow-up, VA was 20/40, but he reported high anxiety after the last injection. He requested switching back to the traditional self-filled aflibercept vial preparation. Before trialing the aflibercept PFS, he had been receiving self-filled intravitreal aflibercept injections for at least 2 years without complication. His vision was hyperopic (spherical equivalent, +2.50 diopters).

Patient 2. A 52-year-old man with phakia underwent intravitreal injection using an aflibercept PFS in the left eye for diabetic macular edema. He previously had undergone pars plana vitrectomy for nonresolving vitreous hemorrhage secondary to proliferative diabetic retinopathy. Before the procedure, VA was 20/70 with IOP of 13 mmHg. Immediately after injection, vision decreased to light perception. Intraocular pressure after injection was measured to be 72 mmHg. Anterior chamber paracentesis was performed to lower the IOP. At follow-up, VA was 20/60. Before

Table 1. Patients Who Experienced Significant Vision Loss Immediately after Intravitreal Injection with Aflibercept Prefilled Syringes

Patient No.	Age (yrs)	Sex	Laterality	Lens Status	Axial Length (mm)	Glaucoma or Ocular Hypertension?	Receiving Topical Intraocular Pressure-Lowering Drops?	Indication for Intravitreal Injection	Anterior Chamber Paracentesis Needed?	Intraocular Pressure before Procedure (mmHg)	Visual Acuity before Procedure	Visual acuity at Next Office Visit	Case Description
1	90	M	—	Pseudophakic	23.76	Y (glaucoma)	Y	AMD	N	—	—	—	• Received >10 prior aflibercept injections without complication
2	85	F	—	Pseudophakic	Right: 24.32 Left: 24.17	N	N	AMD	N	—	—	—	• Received >10 prior aflibercept injections without complication
3	94	F	—	Pseudophakic	—	N	N	AMD	N	—	—	—	• Received >10 prior aflibercept injections without complication
4	46	M	Right	Phakic	—	N	N	PDR/DME	Y	19	20/60	20/40	• Received 2 prior aflibercept, 1 ranibizumab, and 4 bevacizumab injections without complication • Underwent same-day focal laser treatment • Immediate NLP vision with IOP 64 mmHg
5	70	M	Both	Right: pseudophakic Left: phakic	Right: 23.03 Left: 22.56	Y (ocular hypertension)	Y	AMD	N	Right: 17 Left: 19	Right: 20/50 Left: 20/100	Right: 20/50 Left: 20/40	• Unable to drive home for several hours because of profound loss of vision in both eyes

Table 1. (Continued.)

Patient No.	Age (yrs)	Sex	Laterality	Lens Status	Axial Length (mm)	Glaucoma or Ocular Hypertension?	Receiving Topical Intraocular Pressure-Lowering Drops?	Indication for Intravitreal Injection	Anterior Chamber Paracentesis Needed?	Intraocular Pressure before Procedure (mmHg)	Visual Acuity before Procedure	Visual acuity at Next Office Visit	Case Description
6	68	F	—	Phakic	—	N	N	AMD	N	—	—	—	• Received >10 prior aflibercept injections without complication
7	82	F	Right	Pseudophakic	—	N	N	AMD	N	15	20/60	20/60	• Received >10 prior aflibercept injections without complication • IOP 40 mmHg immediately after injection brought down to 25 mmHg with topical IOP-lowering drops
8	52	M	Left	Phakic	—	N	N	PDR/DME	Y	13	20/70	20/60	• Received >10 prior aflibercept injections without complication • Immediate light perception vision with IOP of 72 mmHg

(*Continued*)

Table 1. (Continued.)

Patient No.	Age (yrs)	Sex	Laterality	Lens Status	Axial Length (mm)	Glaucoma or Ocular Hypertension?	Receiving Topical Intraocular Pressure-Lowering Drops?	Indication for Intravitreal Injection	Anterior Chamber Paracentesis Needed?	Intraocular Pressure before Procedure (mmHg)	Visual Acuity before Procedure	Visual acuity at Next Office Visit	Case Description
9	72	M	Right	Phakic	—	N	N	AMD	N	12	20/50	20/40	• Received >10 prior aflibercept injections without complication • Immediate no light perception vision • Requested switch to vial preparation
10	49	M	Right	Phakic	—	N	N	CNV secondary to CSCR	Y	17	20/80	20/70	• Received >10 prior aflibercept injections without complication • Requested switch to vial preparation
11	65	M	Left	Phakic	—	Y (glaucoma suspect)	N	DME	N	16	20/50	20/40	• Received >10 prior aflibercept injections without complication • Requested medication change; now receiving ranibizumab 0.5 mg
12	74	M	Right	Phakic	—	N	N	AMD	Y	18	20/50	20/40	• Received >10 prior aflibercept injections without complication

AMD = age-related macular degeneration; CNV = choroidal neovascularization; CSCR = central serous chorioretinopathy; DME = diabetic macular edema; F = female; IOP = intraocular pressure; M = male; N = no; PDR = proliferative diabetic retinopathy; Y = yes; — = data is unavailable.

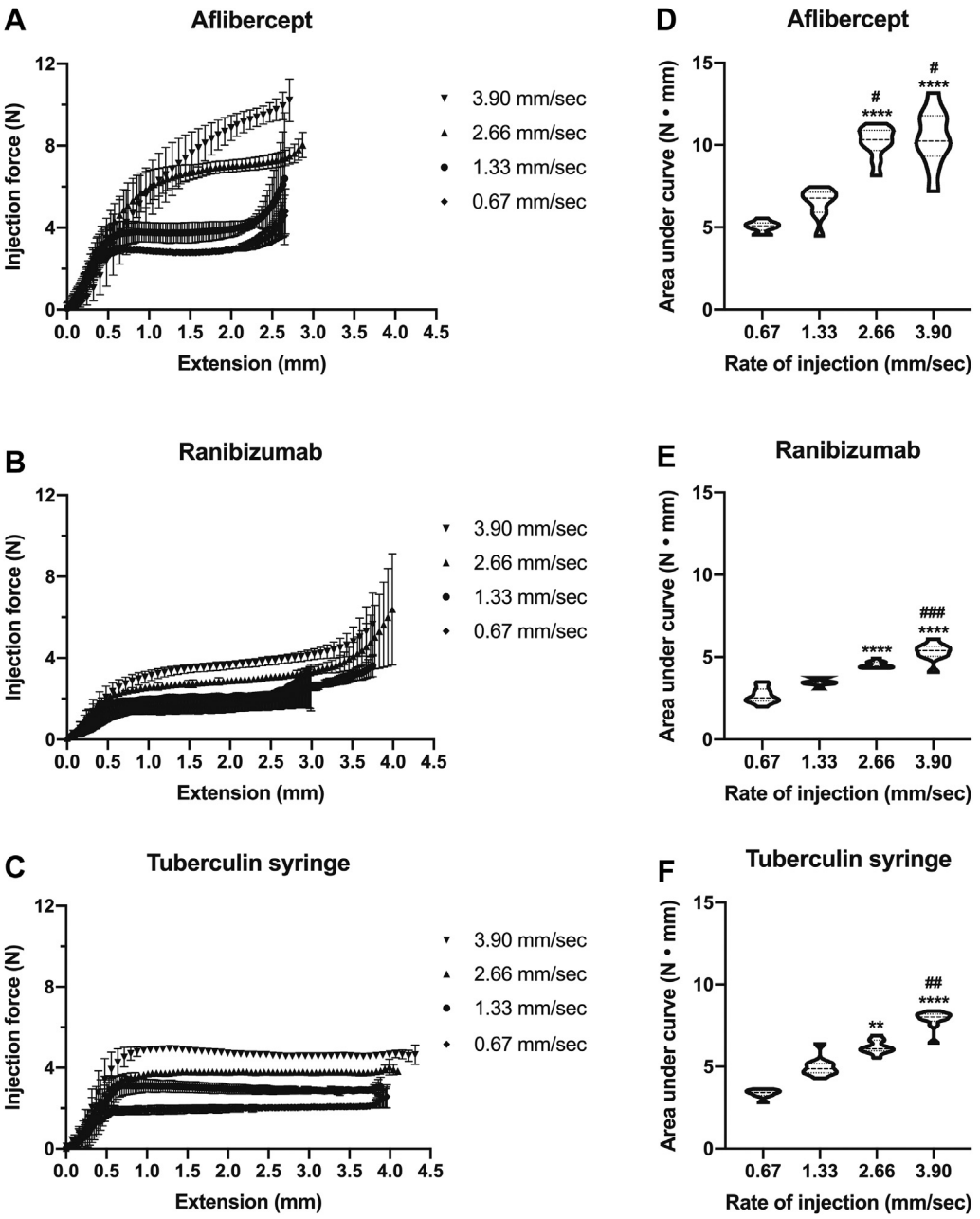

Figure 3. **A**–**C**, Graphs showing average injection force generated with (**A**) aflibercept prefilled syringes, (**B**) ranibizumab prefilled syringes, and (**C**) 1-ml tuberculin syringes at varying injection speeds (0.67 mm/second, 1.33 mm/second, 2.66 mm/second, and 3.90 mm/second). The associated error bars represent standard deviation. **D**–**F**, Graphs showing the area under the receiver operating characteristic curve measured at each injection speed compared for all syringe types. The horizontal dotted lines represent the 25th to 75th percentiles, whereas the dashed line represents median values. $^{**}P < 0.01$ and $^{****}P < 0.0001$ compared with 0.67 mm/second; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, and $^{\#\#\#}P < 0.001$ compared with 1.33 mm/second. N = Newton.

receiving aflibercept via a PFS, he had received self-filled intravitreal aflibercept injections for at least 1 year without complications.

Patient 3. A 70-year-old man underwent intravitreal injections using an aflibercept PFS in both eyes for exudative AMD. He had a history of ocular hypertension that was controlled with topical IOP-lowering medications. He was pseudophakic in the right eye with an axial length of 23.03 mm and phakic in the left eye with an axial length of 22.56 mm. Before the procedure, VA was 20/50 and IOP was 17 mmHg in the right eye and 20/100 and 19 mmHg, respectively, in the left eye. Visual acuity immediately after injection was not documented. However, at the next follow-up visit, the patient reported that he had experienced a 2-hour period of profound vision loss in both eyes that prevented him from driving home. At follow-up, VA was 20/50

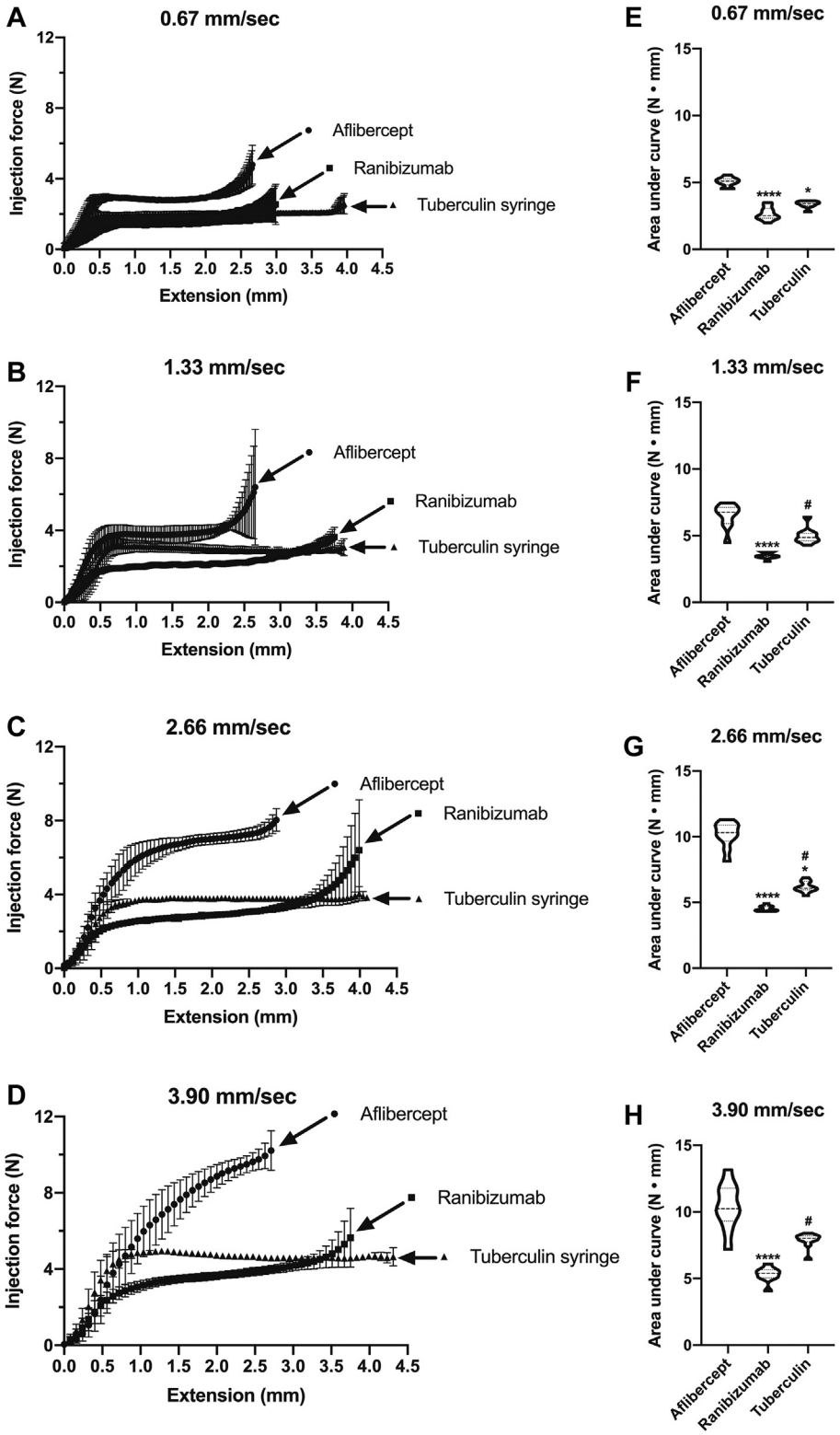

Figure 4. **A**–**D**, Graphs showing comparison of average injection force generated with aflibercept prefilled syringes, ranibizumab prefilled syringes, and 1-ml tuberculin syringes at injection speeds of (**A**) 0.67 mm/second, (**B**) 1.33 mm/second, (**C**) 2.66 mm/second, and (**D**) 3.90 mm/sec. The associated error bars represent 1 standard deviation above and below the mean. **E**–**H**, Graphs showing the area under the receiver operating characteristic curve measured at each injection speed compared for all syringe types. The horizontal dotted lines represent the 25th to 75th percentiles, whereas the dashed line represents median values. *$P < 0.5$ and ****$P < 0.0001$ compared with aflibercept prefilled syringes. #$P < 0.05$ compared with ranibizumab prefilled syringes.

in the right eye and 20/40 in the left eye. Before trialing the aflibercept PFS, he had been receiving self-filled intravitreal aflibercept injections for at least 2 years without complications.

Measuring Injection Force

The injection forces generated with the aflibercept PFS, ranibizumab PFS, and 1-ml tuberculin syringes at 4 different injection speeds are shown in Figures 3 and 4. Comparisons of injection force across different syringes and different speeds were based on the area under the receiver operating characteristic curve for 10 replicates. Higher injection speeds were associated with higher average injection forces for all syringe types (Fig 3). Figure 4 highlights the differences in injection force between different syringe types at different injection speeds. The aflibercept PFS generated significantly more force than the ranibizumab PFS at all injection speeds ($P < 0.0001$; Fig 4). The injection forces generated by the tuberculin syringe were less than those of the aflibercept PFS when the injection speeds were set at 0.67 and 2.66 mm/second ($P < 0.05$; Fig 4). In contrast, the injection forces generated by the tuberculin syringe were more than those of the ranibizumab PFS when the injection speeds were set at 1.33 mm/second, 2.66 mm/second, and 3.90 mm/second ($P < 0.05$; Fig 4).

Discussion

In this study, we examined multiple cases of severe transient vision loss immediately after intravitreal aflibercept PFS use and demonstrated that injection speed and syringe design influence the injection force generated. Overall, our clinical experiences were comparable with those reported in prior literature.[7] Gallagher et al[7] were the first to investigate this. In their case series, 5 eyes demonstrated transient central retinal artery occlusions after injection of aflibercept via PFS, of which 4 eyes underwent anterior chamber paracentesis to normalize IOP. Our study sought to complement their findings by including a more robust study population and to characterize risk factors and clinical outcomes further before and after aflibercept PFS use. Similar to Gallagher et al, all episodes of significant vision loss in our study occurred in patients who previously had received multiple traditional self-filled intravitreal injections without complication. Reassuringly, all patients in our case series showed follow-up VAs that were measured at or better than vision before injection.

Smaller phakic eyes may be more predisposed to IOP spikes after injection with an aflibercept PFS, but the retrospective nature of our study limited our ability to assess these anatomic features further as potential risk factors. In contrast to Gallagher et al,[7] only one-third of the current patients underwent an anterior chamber paracentesis after an IOP spike, which may be attributed to differing practice patterns and comfort level among physicians as well as clinical context, for example, patients with glaucoma or an IOP spike lasting beyond a few minutes. Although anterior chamber paracentesis is not recommended routinely or indicated after an intravitreal injection, it may be considered in certain cases.[13] A notable percentage of the current patients expressed significant injection-related anxiety because of their experience with transient vision loss after aflibercept PFS injection and requested a permanent medication change. Multiple shared negative experiences by patients and physicians with aflibercept PFS have resulted in complete discontinuation of aflibercept PFS use at 1 of our institutions. Our combined experiences suggest that further investigation is needed to elucidate better the risk factors that may predispose patients to transient episodes of significant vision loss.

Prefilled syringes have several advantages over traditional vial packaging (e.g., reduced total injection time, decreased endophthalmitis rates). However, our data demonstrated that the design of the aflibercept PFS may contribute to the episodes of significant severe vision loss observed with its use. Gallagher et al[7] showed that the internal area of the aflibercept PFS lumen was nearly twice that of the 1-ml control syringe, meaning that any unit error in plunger alignment could result in a near 2-fold greater error in volume delivered with the PFS than the control syringe. They determined that, on average, the aflibercept PFS delivered a greater volume than the standard 1-ml control syringe, concluding that any error by the physician to misalign the plunger can result in significant volumetric differences. Several recent reports also have implicated user error as the primary reason for IOP spikes after aflibercept PFS use.[6,8]

Although user error certainly may play a role in the visual outcomes reported in our study, it alone may not explain the entire phenomenon. Our study demonstrated that, even if the plunger is aligned painstakingly with a telecentric lens optical system, more force is still required to depress and inject fully with the aflibercept PFS when compared with other syringe designs. This is consistent with physician feedback recently obtained about the aflibercept PFS in a national survey conducted by our team, in which two-thirds of respondents believed that more force was needed to use the aflibercept PFS when compared with other anti-VEGF preparations (Lee et al, unpublished data, 2021). The increased force needed for an aflibercept PFS may be attributable to its wider-barrel diameter. Injectability at a given constant speed is governed by factors such as needle gauge, which was held constant in our experiment, and surface area of the syringe plunger.[4] Assuming Newtonian behavior, the force exerted on the syringe plunger is directly proportional to the surface area of the syringe plunger, as shown:

$$F = P \times A,$$

where F is the force exerted on the syringe, P is the pressure generated within the syringe barrel, and A is the surface area of the syringe plunger. Because a wider-barrel diameter corresponds to a greater surface area, a larger injection force is generated.[4] Even when accounting for other factors, such as fluid viscosity and non-Newtonian behavior, the syringe barrel diameter is one of the highest-powered

factors related to injection force.[14] Modifications to aflibercept PFS design may help to reduce episodes of transient significant vision loss after injection. Additional factors, such as siliconization and fluid viscosities, should be considered in future studies because they also can influence injectability.[4,15]

Given our findings, we propose several recommendations for ophthalmologists using aflibercept PFS. First, plunger alignment with the mark on the syringe should be confirmed very carefully because a linear relationship exists between volume injected and IOP rise after injection.[7,16] Second, performing intraocular decompression with a cotton tip applicator before intravitreal injection may be considered to reduce the incidence of an IOP spike after injection, although this method has yet to be validated for FPSs in larger prospective studies.[17–19] Third, we recommend injecting at a slower rate. Our data demonstrated that injection speed is directly proportional to injection force; decreasing injection speed by adding 1 extra second may result in significantly lower injection forces. Finally, IOP checks after injection should be considered in all patients who received an aflibercept PFS, especially in patients who are particularly vulnerable to acute IOP spikes, such as individuals with advanced glaucoma.

Our study has several limitations. First, only retina specialists within our 2 institutions were included in our current study, and the clinical outcomes reported herein may not necessarily be generalizable. We sought to address this better by collecting a more representative sample of United States ophthalmologists in a separate study by administering a nationwide online survey querying ophthalmologists on their experiences with the aflibercept PFS (Lee et al, unpublished data, 2021). Second, the results of both studies may be influenced by ascertainment and recall bias, and the accuracy of events may be affected by recent experience. A future prospective comparative analysis may help to address these limitations. Third, the retrospective nature of our case series limited the available clinical data as well as our ability to identify anatomic risk factors that may predispose patients to severe transient vision loss episodes. The retrospective nature also limits our ability to verify the total exact volume injected into the eye by each retina specialist; this could confound our results. However, all syringe volumes were verified before injection in our laboratory-controlled experiment. All aflibercept and ranibizumab PFS used in our laboratory-controlled experiment were previously used syringes, and all anti-VEGF medications were substituted with balanced salt solution; because of this, we were unable to assess the effect of siliconization and differing fluid viscosities on injectability. Additionally, hydrophilic polymer was used in place of ocular tissue in our laboratory-controlled experiment, which does not account for anatomic considerations such as scleral rigidity during intravitreal injections.[20]

In conclusion, retina specialists in our institution have noted numerous cases of severe transient vision loss with the recent adoption of the aflibercept PFS. As a result, some affected patients have reported increased injection-related anxiety. The average injection force may be greater with the aflibercept PFS when compared with other intravitreal anti-VEGF options. Additional clinical studies are needed to understand better how syringe design and fluid dynamics may contribute to vision loss after injection.

Footnotes and Disclosures

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Dr. Scruggs is now affiliated with the Department of Ophthalmology, Mayo Clinic, Rochester, MN.

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HUMAN SUBJECTS: Human subjects were included in this study. Institutional review board approval was obtained at Oregon Health & Science University and at Veteran Affairs Portland Health Care System prior to initiation of this study. All research adhered to the tenets of the Declaration of Helsinki. Informed consent was not necessary because of the retrospective nature of this study.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Lee, Scruggs, Sánchez, Thomas, Faridi

Analysis and interpretation: Lee, Scruggs, Sánchez, Faridi

Data collection: Lee, Scruggs, Sánchez, Faridi

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Overall responsibility: Lee, Scruggs, Sánchez, Thomas, Faridi

Abbreviations and Acronyms:
AMD = age-related macular degeneration; **IOP** = intraocular pressure; **PFS** = prefilled syringe; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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