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RETINAL DISORDERS

Differences in the incidence of aflibercept-related sterile endophthalmitis according to types of disposable syringes used

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Abstract

Purpose To evaluate the difference between the incidences of sterile endophthalmitis after administration of intravitreal aflibercept injection using two different types of syringes.

Methods We administered a total of 498 intravitreal aflibercept injections between September 2017 and August 2021. The disposable syringe used was changed from a 1-mL disposable syringe (Profi syringe, Shinchang Medical., Ltd. Korea) to a 1-mL Becton Dickenson Luer-Lok syringe (BD, Franklin, NJ, USA) in September 2019. Thus, the patients who received injections before and after September 1, 2019, were classified into group 1 and group 2, respectively. The incidence of aflibercept-related sterile endophthalmitis between the two groups was compared.

Results In group 1, six (2.791%) out of 215 cases were diagnosed with sterile endophthalmitis and prescribed topical or oral steroids. In group 2, one (0.353%) out of 283 cases was diagnosed with sterile endophthalmitis and prescribed a steroid eye drop. The incidence of sterile endophthalmitis was significantly different between the two groups ($P = 0.046$).

Conclusion The BD Luer-Lok syringe is associated with a lower incidence of aflibercept-related sterile endophthalmitis than the conventional polypropylene syringe. Differences in immunogenicity associated with silicone oil lubricants within the syringes might be one of the potential reasons behind the difference in the incidence of the sterile endophthalmitis.

Keywords Aflibercept · Intravitreal injection · Sterile endophthalmitis · Silicone oil

Key messages

- Cases of sterile endophthalmitis after intravitreal aflibercept have been reported, and the silicone oil lubricant coated inside the syringe might be one of the possible causes.
- In this report, the authors observed a significant difference in the incidence of sterile endophthalmitis after the change of syringes, and the immunogenicity associated with lubricant seems to play an important role.

Introduction

Intravitreal injection (IVI) is a widely used treatment option for several retinal diseases. IVI of anti-vascular endothelial growth factor (VEGF) agents is a standard treatment for diabetic macular edema (DME), wet age-related macular degeneration (wAMD), retinal vein occlusion, and myopic choroidal neovascularization [1, 2]. Non-infectious sterile inflammation has been reported after IVI of anti-VEGF agents, including bevacizumab (Avastin, Genentech, South San Francisco, CA, USA), ranibizumab (Lucentis, Genentech), and aflibercept (Eylea, Regeneron, Tarrytown, NY, USA) [3–6]. Aflibercept is a humanized recombinant fusion protein [7]. It comprises VEGF receptor 1 and VEGF receptor 2 linked to an Fc fragment of human IgG1 [7]. The fully human antibody is thought to be less immunogenic than

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chimeric antibodies [8]. However, therapeutic monoclonal antibody proteins may possess immunogenicity, which may lead to the development of anti-antibody response [8].

Shortly after the approval of aflibercept, the American Society of Retina Specialists Therapeutic Surveillance Committee reported a cluster of cases of injection-related sterile inflammation [5, 6]. However, the committee did not conclude on the cause of the inflammation.

We observed a decrease in the incidence of sterile inflammation in our clinic after switching the type of syringe used for IVI. Thus, the purpose of this study was to investigate and describe the difference between the incidences of aflibercept-related sterile endophthalmitis among patients who received IVI administered using two different kinds of syringes.

Methods

Patients

This retrospective observational study was conducted according to the tenets of the Declaration of Helsinki. The study was also approved by the Chung-Ang University Hospital Institutional Review Board Committee. All patients who visited the ophthalmology outpatient clinic at the Chung-Ang University Hospital between September 2017 and August 2021 and received an IVI of aflibercept were included in this study. The exclusion criteria were a history of uveitis and administration of aflibercept IVI before or after cataract surgery.

Study protocol

All patients underwent comprehensive ocular examination, including measurement of visual acuity, measurement of intraocular pressure, slit-lamp examination, fundus examination, and swept-source optical coherence tomography (DRI Triton OCT, Topcon, Tokyo, Japan), before the injection.

The vial of aflibercept was stored in the 4 °C refrigerator before use. A topical anesthetic (0.5% proparacaine hydrochloride) and 5% povidone–iodine eye drops were instilled three times every 5 min before the injection. Each patient's eyelid was sterilized with a cotton swab moistened with 10% povidone–iodine. After the eye was held open using a sterile speculum, it was irrigated with 5 cc of povidone-iodine diluted in 5% and 5 cc of physiological saline. The aflibercept was drawn from the vial into a 1-mL disposable syringe through the 19 gauge 1.5-inch filter needle provided with the vial. The needle was then replaced with a Becton Dickenson (BD) 30-gauge needle (PrecisionGlide; BD, Franklin, NJ, USA). Subsequently, aflibercept was injected 3.0–3.5 mm from the limbus under a microscope after gentle agitation to remove air bubbles from the syringe.

In September 2019, the type of disposable syringe used in the hospital was changed from a 1-mL polypropylene syringe (Profi syringe, Shinchang Medical Co. Ltd., Korea) to a 1-mL BD Luer-Lok polycarbonate syringe. Thus, the patients who received an IVI between September 2017 and August 2019 (699 days) and between September 2019 and August 2021 (699 days) were defined as group 1 and group 2, respectively. The eyes registered in group 1 were excluded from group 2, and vice versa.

Evaluation of anterior chamber reaction

The patients who received IVIs were followed up for side effects 1 to 3 days after the injection. Slit-lamp examination and measurement of intraocular pressure were performed during follow-up. Anterior chamber reaction was graded from 0 to 4 + according to the Standardization of Uveitis Nomenclature criteria [9]. The eyes with a positive anterior chamber (A/C) reaction were defined as the eyes with A/C reaction and were re-examined within 3 days. Among them, the eyes that did not show improvement were considered to have aflibercept-related sterile inflammation and were treated using steroid eye drops or oral steroids.

Statistical analysis

Statistical analysis was performed using SPSS software version 20.0 (IBM Corp., Armonk, NY, USA). The chi-square test and Fisher's exact test were used for the evaluation of the study data. *P* values less than 0.05 were considered significant. The incidence of sterile endophthalmitis in group 1 and group 2 was compared.

Results

Baseline characteristics of the patients

A total of 173 eyes that received 500 injections during the two study periods were analyzed in this study. Two injections were excluded because they were administered 1 week after cataract surgery. Thus, a total of 173 eyes of 161 patients that received 498 injections were included. Both eyes were included in 12 patients. The mean age of the patients was 70.82 ± 12.11 years. Baseline visual acuity was 0.49 (20/62) ± 0.34 (logMAR), and the mean intraocular pressure was 14.84 ± 2.97 mmHg. The reasons for injection were macular edema due to retinal vein occlusion (six injections in two eyes, 1.1%), myopic choroidal neovascularization (21 injections in eight eyes, 4.6%), wAMD (395 injections in 121 eyes, 69.9%), DME (64 injections in 31 eyes, 17.9%), and central serous chorioretinopathy (12 injections in 11 eyes, 6.3%). Thus, the mean number of aflibercept

injections administered during the entire study period was 2.86 ± 1.92 per eye. No other significant complications, including infectious endophthalmitis and vitreous hemorrhage, were observed. The baseline characteristics of the patients are shown in Table 1.

Comparison of the anterior chamber reactions of the eyes in the two groups

Between September 2017 and August 2019, 86 eyes of 86 patients were administered 215 IVIs of aflibercept using the conventional polypropylene syringe (Profi syringe, group 1). The mean number of injections administered using this type of syringe was 2.5 ± 1.45 per eye. Between September 2019 and August 2021, 87 eyes of 84 patients were administered 283 aflibercept injections using the new syringe (BD Luer-Lok syringe, group 2). The mean number of injections administered using this type of syringe was 3.25 ± 2.03 per eye. There was no significant difference between the two groups in terms of age and sex. The number of eyes in each group according to diagnosis is also shown in Table 1.

The incidence of sterile endophthalmitis was 2.791% and 0.353% in groups 1 and 2, respectively (Table 2). Comparison of the incidence of A/C reaction revealed a statistically significant difference between the two groups ($P = 0.046$).

Cases of aflibercept-related sterile inflammation

We recorded a total of seven cases (six eyes of six patients) of sterile inflammation. One eye of one patient showed two episodes of sterile endophthalmitis (case 2 and case 4). Five cases were treated for wAMD, whereas two were treated for DME. The logMAR visual acuity of the patients before injection ranged from 0.3–0.9. None of the patients had a history of uveitis or inflammation after IVI of other anti-VEGFs. All patients had previously received aflibercept injections without inflammation, and they complained of cloudy or decreased vision after injection. No patient complained of eyeball pain or conjunctival injection, and no case of hypopyon occurred. The visual acuity of all the patients returned to the baseline value after the injection. The clinical findings of the patients are summarized in Table 3.

Table 2 Comparison of the incidence of anterior chamber reaction and sterile endophthalmitis after intravitreal aflibercept injection

Syringe used for intravitreal aflibercept injection			
	Group 1, Profi syringe	Group 2, Luer-Lok® syringe	*P* value
Total No. of injections	215	283	
No. of sterile endophthalmitis cases (%)	6 (2.791%)	1(0.353%)	*0.046
Average A/C cells	1.5 (range 1 to 3)	2 (2)	†0.571

*Fisher's exact test

†Mann–Whitney *U* test

A/C, anterior chamber

Treatment of sterile endophthalmitis

For treatment of sterile endophthalmitis, oral and topical steroids (PRED FORTE, prednisolone acetate ophthalmic suspension, Allergan, Dublin, Ireland) were administered

Table 1 Demographic data according to the type of syringe used for intravitreal Eylea® injection

Syringe used for intravitreal aflibercept injection			
Variables	Group 1, Profi syringe	Group 2, Luer-Lok® syringe	*P* value
Total no. of patients	86	84	
Total no. of eyes	86	87	
Total no. of injections	215	283	
Age (years)	72.28 ± 11.91	69.38 ± 12.20	*0.152
Male sex	51 (59.3%)	57 (67.9%)	†0.247
Diagnosis			
RVO	0 injection on 0 eyes	6 injections on 2 eyes	
mCNV	10 injections on 5 eyes	11 injections on 3 eyes	
wAMD	179 injections on 65 eyes	216 injections on 56 eyes	
DME	23 injections on 13 eyes	41 injections on 18 eyes	
CSCR	3 injections on 3 eyes	9 injections on 8 eyes	

*Independent *t*-test

†Chi-square test

RVO, retinal vein occlusion; *mCNV*, myopic choroidal neovascularization; *wAMD*, wet age-related macular degeneration; *DME*, diabetic macular edema; *CSCR*, central serous chorioretinopathy

Table 3 Cases of aflibercept-related sterile endophthalmitis

Case	Sex	Age (years)	Diagnosis	Laterality	Baseline LogMAR VA	Previous IVRI	Previous IVBI	Previous IVAI	Syringe	Onset	LogMAR VA	Anterior chamber cells	Vitreous cell	Oral steroid	Eye drops	LogMAR Final VA
1	M	87	wAMD	R	0.4	5	21	2	Profi	4 days	0.4	1 +	2 +	PD 20 mg	Pred 2Q	0.4
2	F	60	DME	R	0.5	0	7	1	Profi	4 days	0.3	1 +	-	-	Pred 2Q	0.3
3	M	76	wAMD	L	0.9	0	0	4	Profi	9 days	0.9	1 +	2 +	PD 20 mg	-	0.9
4	F	60	DME	R	0.4	0	7	4	Profi	3 days	0.7	3 +	NC	PD 20 mg	Lote 2Q	0.3
5	F	90	wAMD	L	0.5	0	0	3	Profi	4 days	0.5	2 +	NC	PD 20 mg	Pred 6	0.5
6	F	72	wAMD	R	0.4	3	0	18	Profi	3 days	1.3	3 +	3 +	PD 20 mg	Pred 2Q	0.4
7	M	77	wAMD	R	0.3	0	3	3	Luer-Lok	4 days	0.3	2 +	NC	-	Pred 2Q	0.3

DME, diabetic macular edema; *IVRI*, intravitreal ranibizumab injection; *IVBI*, intravitreal bevacizumab injection; *IVAI*, intravitreal aflibercept injection; *L*, left; *Lote*, Lotemax eyedrops; *M*, male; *NC*, not checked; *F*, female; *PD*, prednisolone; *Pred*, PRED FORTE eye drops; *R*, right; *wAMD*, wet age-related macular degeneration

in five out of six cases in group 1. The remaining eyes improved after treatment with topical steroid eye drops. The case in group 2 was also treated with only topical steroid eye drops. All cases of decreased or cloudy vision improved, and the visual acuities of the patients reverted to the baseline value after recovery.

Discussion

In this study, we described the differences between the incidences of aflibercept-related sterile inflammation in two groups of patients who were administered IVIs using different types of disposable syringes. Several studies have described sterile inflammation after IVI of aflibercept [3, 5, 6, 10].

Regeneron's postmarking surveillance data indicated a sterile inflammation rate of 0.04% out of over 1 million doses [3]. In their study, Goldberg et al. reported that the overall incidence of sterile inflammation was 20 out of 5,356 injections (0.37%) [3]. Williams et al. reported a higher incidence of sterile inflammation after aflibercept injections (0.16% after 8071 injections) than after bevacizumab (0.10% after 66 356 injections) and ranibizumab (0.02% after 26 161 injections) injections [4]. The variability of the incidence rates reported in these studies (0.04–0.37%) suggests that an unknown cause, as well as aflibercept itself, might be associated with the inflammation. The incidence of sterile inflammation in our clinic was substantially higher (2.791%; six out of 215 injections) than that previously reported, before we changed the type of syringe used.

The BD Luer-Lok syringe is provided with the aflibercept vial as a package in Europe and in the USA. However, the syringe is not provided with the aflibercept vial in South Korea. We previously used the conventional 1-mL polypropylene syringe and switched to a 1-mL BD Luer-Lok polycarbonate syringe in September 2019. After changing the type of syringe, the incidence of sterile inflammation markedly decreased.

The two syringes are different in several aspects, including the material of the syringe body, the disinfection method, additive substances, and the shape of rubber gasket (Table 4, Fig. 1). Thus, these differences may be responsible for the variations in the incidence of sterile endophthalmitis associated with the use of these syringes.

The syringe used for IVI in group 1 was made of polypropylene, whereas that used for group 2 was made of polycarbonate. Polypropylene syringes are widely used because they are inexpensive, generally believed to be inert, and have long-term safety profiles [11, 12]. Thus, it is unlikely that the polypropylene materials are associated with the incidence of sterile inflammation.

Table 4 Features of the two syringes used for intravitreal Eylea® injection

	Profi syringe	Luer-Lok® syringe
Manufacturer	Shinchang Medical Co	Becton/Dickerson
Country of production	Vietnam	USA
Volume	1 mL	
Material of silicone oil used	Dimethylpolysiloxane	
Material of gasket	Latex-free rubber	
Additive substances	1,1-Dichloro-1-fluoroethane	Polyoxyethylene sorbitol ester Polyethylene glycol tert-octylphenyl ether
Material of syringe	Polypropylene	Polycarbonate
Sterilization method	EO gas	Radiation

EO, ethylene oxide

The syringes are usually sterilized using radiation or ethylene oxide (EO) gas. Residual free radicals or residual EO may cause oxidation or protein aggregation of the antibody [13, 14]. However, it is unlikely that the brief duration of exposure between the time the agent is drawn and the time it is injected can cause protein denaturation.

Both types of syringes are coated with the same type of SO (dimethylpolysiloxane) to facilitate the movement of the plunger. The differences in the nature of the SO, presence of impurities, and the amount of the SO within the syringes may influence the occurrence of immune response. Moreover, different kinds of additives are used in each syringe (Table 3). Few previous studies have hypothesized that the cause of aflibercept-related sterile inflammation may be associated with the SO used in the syringe [10, 15, 16]. In the field of pharmaceutical biotechnology, it is well known that SO microdroplets within a syringe induce protein aggregation in solution and are responsible for immune response [16–20]. Proteins in solution are easily absorbed on the surface of SO microdroplets, and SO/protein complexes are readily formed [16, 18]. The SO droplet/protein complexes may be fragmented into aggregates and agglomerates, promoting the formation of impurities [10, 16, 17, 21, 22]. Moreover, SO microdroplets are thought to act as potent immunological adjuvants and can induce antibody responses against a recombinant protein [19, 20]. Some studies have reported that certain syringes are more likely to cause SO microdroplets than others [23–25], which suggests that one syringe can cause a higher incidence of aflibercept-related sterile inflammation than others. In a recent study, Melo et al. demonstrated that post-injection inflammation depends on the type of syringe used; these findings also support our hypothesis [10].

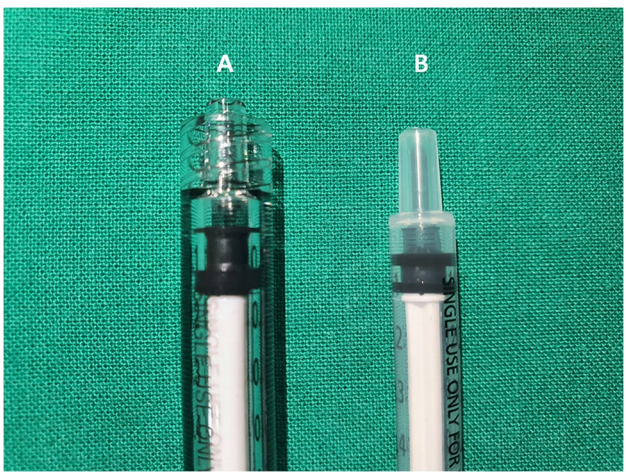

Fig. 1 The two different syringes used in this study. **A** Luer-Lok polycarbonate syringe; **B** conventional polypropylene syringe

Numerous tiny air bubbles are frequently formed within the syringe when aflibercept is drawn from the vial through the 19-gauge filter needle provided [3]. Agitating siliconized syringes to remove the air bubbles induces the formation of particles comprising protein aggregates and SO microdroplets [17]. The presence of air increases the release rate of the SO microdroplets formed by the agitation [25]. Therefore, differences in the immunogenicity of the two syringes, which are associated with SO microdroplets, may be one of the potential causes of the differences in the incidence of sterile inflammation.

Differences in the shape of the plunger tip could also explain the varied incidence of sterile endophthalmitis. The conventional polypropylene syringe has a conical tip, whereas the Luer-Lok polycarbonate syringe has a flat tip (Fig. 1). This morphological difference can cause differences in the amount of SO coated around the plunger tip. It is thought that the angular space between the conical tip and the syringe barrel may be a reservoir for coated SO. Moreover, the conical tip provides a relatively larger contact area between aflibercept and the SO-coated plunger tip than the flat tip. Thus, differences in the shape of the plunger tip may also influence the incidence of inflammation.

Monoclonal antibody therapeutics may cause immunogenicity through the development of an anti-antibody response [8]. However, all the patients who had sterile inflammation in the present study had histories of uneventful aflibercept injection; a finding that is consistent with those of previous reports [3]. Moreover, the eyes with sterile inflammation showed fluid reduction and resolution of macular edema after the injection. Formation of anti-antibody is associated with non-response or reduced response to antibody treatment [26, 27]. Thus, the uneventful ocular histories of the patients and the effectiveness of the injection suggest other causes of sterile inflammation rather than immunogenicity of aflibercept itself.

This study had several limitations. First, this study had a retrospective cross-sectional design; thus, there is a possibility that the results might have been influenced by confounding factors. Injection technique, injection site, disinfection methods, or other unknown factors could be potential causes of sterile endophthalmitis. Second, the number of participants included in the present study is smaller than that of previous studies of aflibercept-related sterile inflammation. The small number might be one of the causes of the high incidence of sterile endophthalmitis in both groups. Third, although the *P* value was less than 0.05, the statistical significance was borderline. This borderline value might also be due to the small number of participants. Fourth, manufacturing lot numbers were not recorded in this study. Fifth, the cause of sterile inflammation was not fully explained in our hypothesis. Although the BD Luer-Lok syringe is provided with the aflibercept vial in the USA, the incidence of sterile inflammation recorded in previous studies varies. However, it should be noted that the BD Luer-Lok syringe releases SO microdroplets as well [25]. Despite the limitations, we evaluated the incidence of aflibercept-related sterile inflammation in clinical settings according to the type of syringe used and attempted to investigate the reason behind the differences in the incidence of inflammation recorded. Additional prospective studies are warranted to confirm our findings.

In conclusion, this study showed that the BD Luer-Lok syringe is associated with a lower incidence of sterile endophthalmitis after aflibercept IVI than the conventional polypropylene syringe. Differences in immunogenicity associated with SO microdroplets in the disposable syringes may be responsible for the differences in the incidence of inflammation. Additionally, flicking the syringe to remove the air bubbles within may also be responsible for the occurrence of sterile inflammation.

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Declarations

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Chung-Ang University Hospital, Seoul, South Korea, and with the 1964 Helsinki declaration.

Informed consent The need for informed consent was waived owing to the retrospective study design.

Conflict of interest The authors declare no competing interest.

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