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Endophthalmitis after Intravitreal Injection of Vascular Endothelial Growth Factor Inhibitors

Management and Visual Outcomes

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Purpose: We describe the presentation of patients developing endophthalmitis after intravitreal injection with vascular endothelial growth factor (VEGF) inhibitors. Moreover, we evaluate the management by comparing the outcomes of immediate tap and injection of intravitreal antibiotics (TAI) versus initial surgical pars plana vitrectomy (PPV). Finally, we analyze the predictive factors of visual outcomes at 6-month follow-up.

Design: Retrospective, single-center, nonrandomized interventional study.

Participants: Patients developing endophthalmitis after receiving an intravitreal injection of anti-VEGF agent between 2006 and 2016.

Methods: All patients received a vitreous biopsy sent for cultures before the initiation of treatment: TAI group versus PPV with intravitreal antibiotics (PPV group).

Main Outcome Measures: Best-corrected visual acuity (BCVA) at 6-month follow-up after treatment for endophthalmitis.

Results: A total of 258 357 intravitreal injections occurred over the course of the 10-year period, of which 40 patients (0.016%) had endophthalmitis within 3 weeks after injection. In total, 34 patients (85.0%) had pain and 25 patients (62.5%) had hypopyon on initial examination. Among 24 culture-positive cases, 66.7% of the causative organisms were coagulase-negative *Staphylococcus*, followed by *Streptococcus* species (10.0%). The best-corrected visual acuity (BCVA) (logarithm of the minimum angle of resolution [logMAR]) at 6-month follow-up was significantly worse for patients who had a positive culture for *Streptococcus* species (4.0; standard deviation [SD], 0.8) (approximately light perception) compared with those who had a positive culture for coagulase-negative *Staphylococcus* (0.4; SD, 0.3) (~20/50) ($P < 0.0001$). Compared with the TAI group, a higher proportion of samples were culture-positive in the PPV group (90.9% vs. 48.3%, $P = 0.03$). There was no statistically significant difference in BCVA at 6-month follow-up between the TAI and PPV groups. Younger age (<85 years) and lower intraocular pressure (IOP) (≤25 mmHg) at presentation were predictive of achieving a BCVA of 20/400 or better at 6-month follow-up after treatment. Initial management (TAI vs. PPV), duration of symptoms, presence of pain, presence of hypopyon, presenting BCVA, and culture status (positive vs. negative) were not found to be predictive of visual outcomes at 6-month follow-up.

Conclusions: No significant difference in BCVA at 6-month follow-up was detected between the TAI and PPV groups. Younger age and lower IOP at presentation were associated with better visual outcomes at 6-month follow-up. *Ophthalmology 2018;125:1279-1286 © 2018 by the American Academy of Ophthalmology*

Intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors is commonly used for exudative age-related macular degeneration (AMD), diabetic macular edema, and retinal vein occlusion. It was projected that more than 6 million anti-VEGF injections would be performed in 2016.[1] The most feared complication of anti-VEGF injections is endophthalmitis, which has an occurrence or incidence ranging from 1 case in 1000 to 1 case in 5000.[2–5] Although endophthalmitis after anti-VEGF injection is uncommon, it can have devastating visual outcomes.

The Endophthalmitis Vitrectomy Study (EVS) has provided us with treatment guidelines for acute endophthalmitis after cataract surgery or secondary intraocular implantation[6]; however, it is unclear how these guidelines can be used for cases after anti-VEGF injection because of differing inoculation pathogenesis and modern vitrectomy techniques.

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To our knowledge, limited studies exist investigating the predictive factors for visual outcomes among patients with endophthalmitis after anti-VEGF injection. Likewise, it is unclear which initial treatment (i.e., vitreous biopsy with intravitreal injection of antibiotics [IIA] vs. pars plana vitrectomy [PPV] with IIA) offers optimal long-term visual outcomes. In our study, we describe the incidence, clinical presentation, and culture status for patients developing endophthalmitis after intravitreal injection. We also compare the visual outcomes of immediate tap and injection of intravitreal antibiotics (TAI) versus PPV as the initial treatment of choice. Finally, we analyze the predictive factors of visual outcome for this challenging group of patients.

Methods

Study Design

A retrospective study was conducted adhering to the tenets of the Declaration of Helsinki with Salus institutional review board approval. This study is HIPAA compliant. The study sample is composed of all patients with endophthalmitis after anti-VEGF injections at a multicentered single subspecialty (retina only) private practice institution (VitreoRetinal Surgery, PA, Minneapolis, MN) over a 10-year period between 2006 and 2016.

Injection Technique

All eyes were injected with an anti-VEGF agent (bevacizumab [Genentech, South San Francisco, CA], ranibizumab [Genentech], or aflibercept [Regeneron, Tarrytown, NY]) in an outpatient clinic setting. Facemasks were not used during the injections; however, talking during the injection by the physician and patient was kept to a minimum. Topical anesthetic drops (proparacaine 0.5%), viscous anesthetic (tetracaine 0.5%), or subconjunctival lidocaine was used to anesthetize the eye before intravitreal injection. Topical 5% povidone-iodine (Betadine) was used to prep the eye by swabbing the eyelashes, caruncle, and upper and lower eyelids followed by the instillation of 1 or 2 drops of topical povidone-iodine solution into the conjunctival cul-de-sac. All anti-VEGF agents were injected through the pars plana using a 30-gauge needle. Variation in the injection technique included differences in injection location (the majority being in the superotemporal quadrant and the minority in the inferotemporal or superonasal quadrants). Another variation of injection technique involved using Betadine liberally on the conjunctiva while the lids were held open with a speculum. Eyelashes were kept out of the field, and no blink was allowed after the last drop of Betadine right before the injection. No topical antibiotic eyedrops were prescribed to the patient after the injection.

Inclusion and Exclusion Criteria

Patient charts were retrospectively reviewed. Only cases with presumptive endophthalmitis after anti-VEGF injections were included, and the endophthalmitis had to have occurred within 3 weeks of intravitreal injection. All patients received vitreous biopsy ("tap") before the initiation of the treatment, and the collected sample was sent for microbial culture. All patients received treatments the same day when they presented to the clinic with presumed endophthalmitis.

This study is a nonrandomized interventional study. The treatment decisions (IIA vs. PPV with IIA) were based on the clinical judgment of the treating physicians. This retrospective study was based on the initial treatment that patients received, and patients were categorized into the TAI group (received IIA only) or the PPV group (first received PPV with intraocular antibiotics).

Patients who had intravitreal injection of medications other than anti-VEGF agent, such as triamcinolone, were excluded. Those who had a history of any intraocular or extraocular surgery within 1 year of receiving the last intravitreal injection of anti-VEGF agent were excluded. Cases were excluded if endophthalmitis developed after a history of trauma.

Tap and Injection of Intravitreal Antibiotics Group

All eyes in this group received immediate diagnostic vitreous biopsy ("tap") through the pars plana followed by injection of intravitreal antibiotics. The vitreous biopsy consisted of insertion of a short 25- or 27-gauge needle into the vitreous cavity to aspirate a vitreous sample. If an adequate vitreous sample could not be obtained, an aqueous tap was then performed via a short 30-gauge needle at the corneal limbus. All collected specimens were sent for gram stain, cultures, and sensitivities. Patients were given intravitreal injections of vancomycin (1 mg/0.1 ml) and ceftazidime (2.25 mg/0.1 ml). Intravitreal dexamethasone was not administered any cases. Topical steroid and antibiotic drops were also prescribed at the discretion of the treating physician, and patients were followed daily until they improved clinically. The drops were tapered as deemed necessary, and examination intervals were extended.

Pars Plana Vitrectomy Group

Patients in this group were transferred to the operating room on the same day of diagnosis. A retrobulbar block was placed in the periorbital space for anesthesia. The eye was then prepped and draped in usual sterile fashion, and a lid speculum was inserted.

Pars plana vitrectomy (23- or 25-gauge) was performed, and all unopacified vitreous and any vitreous membranes present were removed with the vitreous cutter. A vitreous sample with the infusion line turned off was sent for culture at the start of the surgery. Peripheral vitreous was then removed with the vitreous cutter and with aid of scleral indentation.

Inspection was performed, and any retinal breaks (if present) were demarcated with laser retinopexy. A partial or complete air−fluid exchange was performed at the discretion of the attending surgeon. Any leaking sclerotomy sites were sutured. At the conclusion of the case, 0.1 ml of vancomycin (1.0 mg/0.1 ml) and 0.1 ml of ceftazidime (2.25 mg/0.1 ml) were injected through the pars plana with a short 30-gauge needle.

Variables of Interest

Patient characteristics included age, sex, cigarette smoking status (past or present), and clinical diagnosis (indication for injection). Signs, symptoms, and clinical findings on presentation included pain, hypopyon, Snellen best-corrected visual acuity (BCVA) on presentation using logarithm of the minimum angle of resolution (logMAR) visual acuity, intraocular pressure (IOP), duration of endophthalmitis symptoms (e.g., pain, redness, vision loss, or floaters) before presentation, and the time between last injection of anti-VEGF agent and symptoms.

In addition, information about the anti-VEGF agents that the patient last received (bevacizumab, ranibizumab, or aflibercept), total number of injections received for each patient, culture growth results, initial treatment (IIA vs. PPV with intraocular antibiotics), and follow-up time were also collected. The difference of BCVA

(logMAR) at 6-month follow-up after treatment for endophthalmitis versus initial presentation was used to determine the change of BCVA.

Statistical Analysis

The primary end point variable in this study was BCVA achieved at 6-month follow-up after treatment for endophthalmitis. All statistical analyses were performed using SAS Version 9.3 (SAS Institute, Inc, Cary, NC). Descriptive analysis was used to describe the sample characteristics. Continuous variables were described by using means and standard deviation (SD) or median and interquartile range. Categoric variables were described by using frequencies and percentages (%). To compare different groups in categoric variables, chi-square tests or Fisher exact tests (n <5) were used, and *t* tests were used to compare the means for different categories.

Spearman correlation coefficient was used to assess the correlation between continuous variables and the BCVA at 6-month follow-up using logMAR. Logistic regression analysis was undertaken to assess categoric factors associated with a visual acuity of 20/400 or better at 6-month follow-up after treatment. For the univariate logistic regression analysis, each variable of interest was considered separately in a model to predict final visual acuity of 20/400 or better. Crude odds ratio (COR) and 95% confidence interval (CI) were obtained for each factor. Subsequently, multivariable logistic regression models were used to identify possible predicative factors for a visual acuity of 20/400 or better at 6-month follow-up. Adjusted odds ratio (AOR) and 95% CI were obtained for each factor in the multivariable logistic regression analysis. Factors with a 2-tailed P value < 0.05 were considered significant. The area under the receiver operating characteristic curve and Hosmer–Lemeshow statistic were calculated to determine goodness-of-fit of the multivariable logistic regression model.

Results

A total of 40 patients (0.016%) developed endophthalmitis after 258 357 anti-VEGF agent injections during a 10-year period (2006–2016). The mean age of the study sample was 81.4 years (SD, 10.9), and 67.5% of the patients were female. A small percentage of patients were smokers (12.5%).

The majority of patients received anti-VEGF agents for exudative AMD (72.5%), followed by diabetic macular edema (15.0%) and retinal vein occlusion (12.5%). The average total number of injections of anti-VEGF agents for each patient was 14.4 (SD, 11.6). Among those patients who experienced endophthalmitis after injection, 23 (57.5%) received bevacizumab, 9 (22.5%) received ranibizumab, and 8 (20.0%) received aflibercept as the last anti-VEGF agent injected.

Mean BCVA (logMAR) before the occurrence of endophthalmitis was 0.5 (SD, 0.4) (~20/60) when patients received the last intravitreal anti-VEGF injection. Before developing endophthalmitis, 13 patients (32.5%) had 20/20 to 20/40 vision, 18 patients (45.0%) had 20/50 to 20/80 vision, 5 patients (12.5%) had 20/100 to 20/200 vision, 3 patients (7.5%) had 20/400 vision, and 1 patient (2.5%) had counting fingers (CF) vision. There was no statistical difference for mean BCVA (logMAR) before the occurrence of endophthalmitis between the TAI group (0.5; SD, 0.4) and the PPV group (0.5; SD, 0.3) ($P = 0.81$).

The mean time between anti-VEGF agent injection and endophthalmitis symptoms was 3.8 days (SD, 2.0). The mean duration of endophthalmitis symptoms before presentation was 4.4 days (SD, 2.0). At initial presentation, the mean BCVA (logMAR) was 2.4 (SD, 1.1) (approximately CF to hand motions [HM]). In total, 8 patients (20.0%) had a BCVA of 20/400 or better, and 32 patients (80%) had a BCVA worse than 20/400 (CF, 12 [37.5%]; HM, 15 [46.9%]; light perception, 4 [12.5%]; and no light perception, 1 [3.1%]). The mean IOP was 19.6 mmHg (SD, 12.3) at presentation. On slit-lamp and funduscopic examination, 34 patients (85.0%) had pain and 25 patients (62.5%) had hypopyon on initial examination.

At 6-month follow-up, the majority (32 patients [80.0%]) of patients achieved a BCVA of 20/400 or better, and 8 patients (20.0%) had a BCVA worse than 20/400 (CF, 2 [5.0%]; HM, 2 [5.0%]; light perception, 3 [7.5%]; no light perception, 1 [2.5%]). Compared with the BCVA when patients received their last intravitreal injection of anti-VEGF agent before developing endophthalmitis, 9 patients (22.5%) had improved BCVA at 6-month follow-up, 11 patients (27.5%) had the same BCVA at 6-month follow-up, and 20 patients (50.0%) had worse BCVA at 6-month follow-up. Compared with the initial presentation, 32 patients (80.0%) had improved BCVA at 6-month follow-up, 5 patients (12.5%) had the same BCVA at 6-month follow-up, and 3 patients (7.5%) had worse BCVA at 6-month follow-up.

Regarding microbiology testing, 24 (60.0%) were culture-positive and 16 (40.0%) were culture-negative. Among those who were culture-positive, 16 patients (66.7%) grew coagulase-negative *Staphylococcus*, followed by *Streptococcus* species (n = 4, 16.7%), *Haemophilus influenzae* (n = 1, 4.2%), *Erysipelothrix rhusiopathiae* (n = 1, 4.2%), *Serratia marcescens* (n = 1, 4.2%), and *Enterococcus faecalis* (n = 1, 4.2%). The BCVA (logMAR) at 6-month follow-up was significantly worse for patients who had a positive culture for *Streptococcus* species (4.0; SD, 0.8) (approximately light perception) compared with those who had a positive culture for coagulase-negative *Staphylococcus* (0.4; SD, 0.3) (~20/50) ($P < 0.001$). In addition, the BCVA (logMAR) at 6-month follow-up was significantly worse for patients who had a positive culture for other than coagulase-negative *Staphylococcus* (2.0; SD, 0.8) (approximately CF) compared with those who had a positive culture for coagulase-negative *Staphylococcus* (0.4; SD, 0.3) (~20/50) ($P = 0.002$).

Regarding the endophthalmitis treatment groups, 72.5% of the patients received IIA only (TAI group) and 27.5% had immediate PPV with intraocular antibiotics (PPV group). Table 1 shows that there was no statistical difference in age, sex, clinical diagnosis, anti-VEGF agent received, total number of injections of anti-VEGF agents, presenting BCVA, presenting IOP, pain, hypopyon, time between last intravitreal anti-VEGF agent injection, and the initial endophthalmitis symptoms between the TAI group and the PPV group. However, the time between endophthalmitis symptoms and the initial treatment was shorter for the PPV group compared with the TAI group (3.1 days [SD, 1.4] vs. 4.8 days [SD, 2.0], $P = 0.012$). All patients (100%) in the PPV group had successful biopsy, and 25 patients (86.2%) in the TAI group had successful vitreous biopsy; 4 patients (13.7%) in the TAI group needed additional anterior chamber tap. Compared with the TAI group, a higher proportion of samples were culture positive in the PPV group (90.9% vs. 48.3%, $P = 0.03$).

Table 2 shows that there was no statistically significant difference in BCVA at 6-month follow-up and improvement of vision from presentation to 6-month follow-up between the TAI group and PPV group. When considering BCVA at 6-month follow-up compared with BCVA before the occurrence of endophthalmitis (i.e., BCVA when patients received their last intravitreal injection of anti-VEGF agent), a higher proportion of patients in the PPV group (27.3%) had improved vision compared with the TAI group (20.7%) ($P = 0.69$).

Table 1. Characteristics of Study Patients Stratified by Initial Treatment at Presentation

Characteristic	TAI Group (n = 29)		PPV Group (n = 11)		P Value
	Mean (SD)	*Frequency (%)*	*Mean (SD)*	*Frequency (%)*	
Age (yrs)	81.5 (11.0)		80.8 (11.0)		0.85
<85		15 (51.7)		6 (54.6)	0.87
≥85		14 (48.3)		5 (45.4)	
Sex					0.29
Male		11 (37.9)		2 (18.2)	
Female		18 (62.1)		9 (81.8)	
Clinical diagnosis					0.37
Age-related macular degeneration		20 (69.0)		9 (81.8)	
Diabetic macular edema		5 (17.2)		1 (9.1)	
Retinal vein occlusion		4 (13.8)		1 (9.1)	
Smoker					
Yes		4 (13.8)		1 (9.1)	0.69
Total No. of intravitreal anti-VEGF injections	13.9 (11.1)		15.7 (13.4)		0.67
Last intravitreal anti-VEGF injection					0.70
Bevacizumab		17 (58.6)		6 (54.6)	
Ranibizumab		5 (17.3)		4 (36.4)	
Aflibercept		7 (24.1)		1 (9.0)	
Time between last intravitreal anti-VEGF injection and the initial endophthalmitis symptom(s) (days)	4.0 (1.8)		3.1 (1.4)		0.13
Time between initial endophthalmitis symptom(s) and initial treatment (days)	4.8 (2.0)		3.1 (1.4)		0.01
BCVA (logMAR)	2.2 (1.0)		2.9 (1.0)		0.06
≥20/400		8 (27.6)		0 (0.0)	
<20/400					
CF		9 (42.9)		3 (27.2)	
HM		9 (42.9)		6 (54.6)	
Light perception		3 (14.3)		1 (9.1)	
No light perception		0 (0.0)		1 (9.1)	
IOP (mmHg)	18.4 (10.9)		22.6 (15.6)		0.34
6–25 mmHg		25 (86.2)		8 (72.7)	
>25 mmHg		4 (13.8)		3 (27.3)	
Pain					
Yes		23 (79.3)		11 (100.0)	0.16
Hypopyon					
Yes		17 (58.6)		8 (72.7)	0.49

BCVA = best-corrected visual acuity; CF = counting fingers; HM = hand motions; IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution; PPV = pars plana vitrectomy; SD = standard deviation; TAI = tap and injection of intravitreal antibiotics; VEGF = vascular endothelial growth factor.

At presentation, cases with a positive microbial culture had a worse mean presenting BCVA (logMAR, 2.8 [SD, 1.0] vs. 1.7 [SD, 0.9], $P = 0.002$) compared with those with a negative culture. Those with a positive culture also had a higher mean IOP (22.9 [SD, 14.8] vs. 14.7 [SD, 3.8], $P = 0.02$). A higher proportion of patients with a positive culture had pain compared with those with a negative culture (95.8% vs. 68.7%, $P = 0.03$). Between culture-positive and culture-negative cases, there was no statistical difference in age, sex, total number of intravitreal injections received, time between last intravitreal anti-VEGF agent injection and the initial endophthalmitis symptoms, duration between endophthalmitis symptoms and initial treatment, presence of hypopyon, BCVA at a 6-month follow-up, improvement of vision from presentation to a 6-month follow-up, and follow-up duration.

Among those patients who did not have an improvement in visual acuity at the 6-month follow-up, there was a higher mean age, 91.3 years (SD, 5.3) versus 78.9 years (SD, 10.5), and a higher mean IOP, 29.0 mmHg (SD, 17.2) versus 17.3 mmHg (SD, 9.7). There was no difference in sex, total number of intravitreal injections of anti-VEGF received, time between last intravitreal anti-VEGF agent injection and the initial endophthalmitis symptoms, duration between endophthalmitis symptoms and injection, duration of the symptoms and treatment, presence of pain, or presence of hypopyon between those who had an improvement in visual acuity at the 6-month follow-up compared with those who did not.

A correlation was found between BCVA (logMAR) at the 6-month follow-up and age (Spearman's rank correlation coefficient = 0.4886, $P = 0.001$), as well as presenting IOP (Spearman's rank correlation coefficient = 0.4803, $P = 0.002$). However, neither the duration between endophthalmitis symptoms and initial treatment (Spearman's rank correlation coefficient = −0.02668, $P = 0.87$) nor the BCVA on presentation (logMAR) (Spearman's rank correlation coefficient = 0.2798, $P = 0.08$) was correlated with BCVA (logMAR) at the 6-month follow-up. A negative correlation was found between the change of BCVA and the age (Spearman's rank correlation coefficient = −0.4371, $P = 0.005$). In addition, the presenting BCVA (logMAR) was correlated with the change of BCVA (logMAR) (Spearman's rank correlation coefficient = 0.4716, $P = 0.002$).

In the univariate logistic regression analysis (Table 3), patients who were aged less than 85 years were 11.7 times (COR; 95% CI, 1.3–106.8; $P = 0.03$) more likely to achieve a BCVA of 20/400 or better at the 6-month follow-up compared with those who were aged 85 years or older. Patients who had an IOP of 25 mmHg or lower were 30.0 times (COR; 95% CI, 3.3–189.2; $P = 0.002$)

Table 2. Visual Outcomes at 6-Month Follow-up Stratified by Initial Treatment

Characteristic	TAI Group (n = 29)		PPV Group (n = 11)		P Value
	Mean (SD)	*Frequency (%)*	*Mean (SD)*	*Frequency (%)*	
BCVA at 6-mo follow-up (logMAR)	0.9 (0.9)		1.7 (1.9)		0.06
20/400 or better		25 (86.2)		7 (63.6)	
Worse than 20/400					
CF		2 (6.9)		0 (0.0)	
HM		1 (3.4)		1 (9.1)	
Light perception		1 (3.4)		2 (18.2)	
No light perception		0 (0.0)		1 (9.1)	
BCVA at 6-mo follow-up compared with BCVA before the occurrence of endophthalmitis when patients received last intravitreal anti-VEGF injection					0.69
Improved		6 (20.7)		3 (27.3)	
No change or worse		23 (79.3)		8 (72.7)	
BCVA at 6-mo follow-up compared with presenting BCVA					0.18
Improved		25 (86.2)		7 (63.6)	
No change or worse		4 (13.8)		4 (36.4)	

BCVA = best-corrected visual acuity; CF = counting fingers; HM = hand motions; logMAR = logarithm of the minimum angle of resolution; PPV = pars plana vitrectomy; SD = standard deviation; TAI = tap and injection of intravitreal antibiotics; VEGF = vascular endothelial growth factor.

more likely to achieve a BCVA of 20/400 or better at the 6-month follow-up compared with those with a higher IOP. The initial treatment (TAI vs. PPV), presence of pain, presence of hypopyon, presenting BCVA, culture status (positive vs. negative), and duration between endophthalmitis symptoms and initial treatment were not found to be predictive of a BCVA of 20/400 or better after treatment at the 6-month follow-up (Table 3).

The results of multivariable logistic regression analysis are shown in Table 4. In the multivariable logistic regression analysis, adjusted for the time between initial endophthalmitis symptom and initial treatment, patients who had an IOP of 25 mmHg or lower were 40.8 times (AOR; 95% CI, 2.1–792.5; $P = 0.01$) more likely to achieve a BCVA of 20/400 or better at the 6-month follow-up compared with those with a higher IOP; those patients who were younger than 85 years of age were 22.1 times (AOR; 95% CI, 1.1–487.3; $P = 0.04$) more likely to achieve a BCVA of 20/400 or better at the 6-month follow-up compared with those who were aged 85 years or older. The area under the receiver operating characteristic curve was 0.93, and the Hosmer–Lemeshow statistic ($P = 0.85$) suggested adequate mode fit.

Discussion

In our study, the incidence of endophthalmitis after intravitreal anti-VEGF agent injection was 0.016%, which is comparable to the incidences reported in the literature.[3,7–9] Younger age and lower IOP at presentation were predictive of achieving a BCVA of 20/400 or better at the 6-month follow-up after treatment. There was no statistical difference in BCVA at 6-month follow-up after treatment or change in vision between the TAI and PPV groups.

Patients who were younger than 85 years of age had better BCVA at 6-month follow-up and a higher proportion of improvement in BCVA at 6-month follow-up. This might suggest that older patients presented with more advanced disease requiring more treatments of anti-VEGF agents. However, there was no correlation found between the age and the total number of injections of anti-VEGF agents (Spearman's rank correlation coefficient = 0.07493, $P = 0.65$). Our results coincide with those of the EVS, which found that older age was associated with decreased final visual acuity.[6]

In the EVS, patients with a presenting IOP >25 mmHg were 1.4 times more likely to experience a decrease in vision compared with those with an IOP between 5 and 25 mmHg.[6] In our study, we see a similar relationship because cases with an IOP >25 mmHg were 40.8 times (95% CI, 2.1–792.5) less likely to achieve a BCVA of 20/400 or better at the 6-month follow-up, compared with those with a lower presenting IOP between 5 and 25 mmHg ($P = 0.01$). This relationship was further confirmed in the subgroup analysis among cases with a positive culture in our study (COR, 18.8; 95% CI, 2.1–170.2; $P = 0.009$). Our analysis also showed that the presenting IOP was significantly lower for those with an improved vision compared with cases without improvement in vision after endophthalmitis treatment. These results suggest that in the context of endophthalmitis, an abnormally presenting high IOP is correlated with a worse visual acuity. This is clinically significant and can aid in prognostication of outcomes when patients are first diagnosed with endophthalmitis. Although it is possible that elevated IOP can contribute to existing optic neuropathy, elevated IOP may be a surrogate marker of increased inflammation with infection.

A higher proportion of samples were cultured positive in the PPV group compared with the TAI group. This might indicate that vitreous samples from PPV are more likely to obtain an adequate sample for culture compared with vitreous tap or anterior chamber tap. In addition, this might also suggest the potential selection bias that more severe cases at presentation underwent PPV.

In our study, 80% of the cases presented with a BCVA worse than 20/400. However, the majority of the patients (80.0%) achieved a BCVA of 20/400 or better at the 6-month follow-up after treatment. Specifically, 8 patients (20.0%) had a BCVA of 20/40 or better, 16 patients (40.0%)

Table 3. Univariate Logistic Regression Analysis: Predictive Factors of Best-Corrected Visual Acuity 20/400 or Better at 6-Month Follow-up

Variables	COR (95% CI)	P Value
Age (yrs)		
<85	11.7 (1.3–106.8)	0.03
≥85	1.0	
Sex		
Male	11.8 (0.6–246.7)	0.11
Female	1.0	
Last intravitreal anti-VEGF injection		
Bevacizumab	1.0 (0.2–6.2)	0.72
Ranibizumab	1.9 (0.2–19.7)	0.56
Aflibercept	1.0	
BCVA at initial presentation		
20/400 or better	5.9 (0.3–134.4)	0.27
Worse than 20/400	1.0	
IOP at initial presentation (mmHg)		
≤25 mmHg	30.0 (3.3–189.2)	0.002
>25 mmHg	1.0	
Pain		
No	1.3 (0.1–13.0)	0.83
Yes	1.0	
Hypopyon		
No	2.1 (0.4–11.8)	0.42
Yes	1.0	
Time between initial endophthalmitis symptom(s) and initial treatment (days)		
>2 days	4.2 (0.7–24.8)	0.11
≤2 days	1.0	
Initial treatment		
TAI	3.6 (0.7–18.0)	0.12
PPV with intravitreal antibiotics injections	1.0	
Culture status		
Culture negative	6.2 (0.7–56.2)	0.11
Culture positive	1.0	

BCVA = best-corrected visual acuity; CI = confidence interval; COR = crude odds ratio; IOP = intraocular pressure; PPV = pars plana vitrectomy; TAI = tap and injection of intravitreal antibiotics; VEGF = vascular endothelial growth factor.

Table 4. Multivariable Logistic Regression Analysis: Predictive Factors of Best-Corrected Visual Acuity 20/400 or Better at 6-Month Follow-up

Variables	AOR (95% CI)	P Value
Age (yrs)		
<85	22.1 (1.1–487.3)	0.04
≥85	1.0	
IOP at initial presentation (mmHg)		
≤25 mmHg	40.8 (2.1–792.5)	0.01
>25 mmHg	1.0	
Time between initial endophthalmitis symptom(s) and initial treatment (days)		
>2 days	4.2 (0.4–41.2)	0.21
≤2 days	1.0	

AOR = adjusted odds ratio; CI = confidence interval; IOP = intraocular pressure.

had a final BCVA between 20/50 and 20/100, 5 patients (12.5%) had a final BCVA between 20/125 and 20/200, and 11 patients (27.5%) had a final BCVA of 20/400 or worse. There was no statistical difference in the BCVA at presentation or at the 6-month follow-up between the TAI group and the PPV group. However, there was a nonstatistically significant trend that the PPV group had a worse BCVA both on presentation and at the 6-month follow-up after treatment but also demonstrated a larger improvement in vision when comparing BCVA before endophthalmitis and BCVA at the 6-month follow-up. All patients in the PPV group had a visual acuity worse than 20/400, and 72.8% of them had HM or worse vision on presentation. This may represent a selection bias that relegated eyes with worse vision and more advanced disease in the PPV group, whereas the TAI group had less severe disease. This hypothesis is congruent with the fact that more severe disease in the PPV group had worse associated presenting BCVA and was due to more severe ocular infection and inflammation with earlier presentation (3.1 vs. 4.8 days, $P < 0.05$). Although there was no statistical difference in visual outcome detected between the TAI group and PPV group, we are not able to conclude the equality of TAI compared with PPV with IIA for endophthalmitis after intravitreal injections because this is a nonrandomized study and potential selection bias exists.

There is no established treatment protocol for endophthalmitis after intravitreal injection of an anti-VEGF agent, unlike endophthalmitis after cataract extraction in which specific guidelines were developed by the EVS.[6] In a previous study of 23 cases of post–anti-VEGF injection endophthalmitis, 90% of the patients in the TAI group regained visual acuity within 1 line or better of baseline compared with 46% cases in the PPV group.[10] In our study, we compared the difference between BCVA at the 6-month follow-up after treatment and presenting BCVA (change of visual acuity) and found that there was no statistical difference in the proportion of patients who had improved vision after treatment between the TAI and PPV groups. In addition, there was no statistical difference detected in the change of visual acuity between those 2 groups (TAI vs. PPV: 1.3 vs. 1.2 logMAR, $P = 0.78$).

Immediate PPV should be considered for eyes with severe inflammation and very poor initial vision because our data may have biased these more severe cases to the PPV group. Therefore, for more severe cases, PPV might be considered as the initial treatment. Furthermore, because this was a retrospective study, we are not able to make a specific recommendation; ideally, a multicenter, prospective randomized study is needed to further explore the effect of TAI versus PPV as the initial treatment in cases of endophthalmitis after intravitreal anti-VEGF injection. However, the low incidence of endophthalmitis after anti-VEGF injections continues to hinder the feasibility of these studies.

Compared with patients with a negative culture, patients with a positive culture had a significantly worse BCVA (2.8 vs. 1.7 logMAR, $P = 0.002$), a higher IOP (22.9 vs. 14.7 mmHg, $P = 0.02$), and a higher proportion of pain (95.8% vs. 68.7%, $P = 0.004$) at presentation. These factors suggest

that virulent infection is associated with severe inflammation. Similar to a previously published report,[7] our study found no difference in the proportion of culture-negative cases after bevacizumab injection versus ranibizumab injection. Our study is also able to conclude that there was no difference in the proportion of culture-negative cases after bevacizumab injection versus aflibercept injection.

In this study, 66.7% of patients with a positive culture had a hypopyon versus 56.3% cases with a negative culture. The presence of hypopyon was more than doubled compared with the finding of 20.5% culture-positive cases with a hypopyon after anti-VEGF injections from a prior study.[11] However, the presence of hypopyon in our data was less than the reported proportion of 80% among patients with biopsy-proven endophthalmitis after cataract surgery.[12] A proposed explanation for the lower proportion of hypopyon for cases after anti-VEGF injections relates to the concept that after intravitreal injection, the initial insult causes vitreal inflammation, whereas after cataract surgery, it is the anterior chamber that is the suspected initial site of inflammation.

The EVS showed that 70% of cases of culture-positive endophthalmitis were caused by coagulase-negative *Staphylococcus*.[6] In a meta-analysis of 50 cases of endophthalmitis after anti-VEGF injection,[13] 65.4% of the causative organisms were coagulase-negative *Staphylococcus* among 26 culture-positive isolates. In our study, among those with a positive culture, a similar percentage (66.7%) of cases was affected by the coagulase-negative *Staphylococcus*. Our study is further evidence for coagulase-negative staphylococci, which constitute normal flora of human skin, as the most common causative organism for endophthalmitis after intravitreal injection.[14] Logically, it supports the importance of proper aseptic technique to prevent endophthalmitis after intravitreal injection. Topical povidone–iodine is the only proven form of endophthalmitis prophylaxis.[15,16] It is important to note that povidone–iodine should be instilled on the ocular surface before the application of a topical viscous anesthetic agent because the latter is known to form a barrier affecting povidone–iodine contact and killing time with conjunctival bacteria.[17]

In the EVS, the rate of *Streptococcus*-associated postoperative endophthalmitis was 9.0% among culture-positive endophthalmitis cases.[6] In previous studies, *Streptococcus* accounted for 30.8% and 24.4% of culture-positive cases after anti-VEGF injection.[11,13] In addition, an increase in *Streptococcal* endophthalmitis after intravitreal injections was found compared with after cataract surgery.[18,19] In our study, *Streptococcus* accounted for 16.7% of the culture-positive cases. The higher rate of postinjection endophthalmitis from *Streptococcus* suggests that the spectrum of organisms in the clinic is different than in the operating room setting and that *Streptococcus* species are more common causatives of endophthalmitis after intravitreal injection. The higher percentage of *Streptococcus* in postinjection endophthalmitis might reflect on the possibility of aerosol contamination of the surgical field by respiratory flora previously suggested by McCannel.[13] We also found that patients with a positive culture for *Streptococcus* species had a significantly worse BCVA at 6-month follow-up after treatment compared with those with a positive culture for coagulase-negative *Staphylococcus*. Thus, measures to reduce potential infections by restricting talking by the patient and provider during the procedure should be implemented.

There were 16 cases (40%) without microbial growth in culture specimens. Among these, 15 patients had TAI and 1 patient had PPV plus intraocular antibiotics as initial treatment. It was reported that the symptoms started at an average of 2.55 days (range, 1–6 days) after injection in the endophthalmitis group and less than 1 day in the acute intraocular inflammation group.[20] In our study, the symptoms started at an average of 4.1 (SD, 1.8) days for cases with a negative culture. Specifically, 1 patient (6.3%) had symptoms 1 day after the injection, 3 patients (18.7%) had symptoms 2 days after the injection, and 2 patients (12.5%) had symptoms 3 days after the injection. Taken in aggregate, these data show that 10 patients (62.5%) with endophthalmitis after intravitreal injection had symptoms within 4 days of the injection. This is further evidence of heightened awareness of abnormal symptoms in the days after intravitreal injection.

There are several limitations in our study. First, the data were collected retrospectively and, as such, are limited to biases inherent in this type of data collection. Second, this is a nonrandomized study with possible selection bias that more advanced disease was included in the PPV group, whereas the TAI group had less severe disease. Therefore, we cannot conclude the equality of TAI compared with PPV with IIA for endophthalmitis after intravitreal injections. Third, our sample size is relatively small given this uncommon condition. In addition, we used BCVA at a 6-month follow-up after treatment as the main outcome measure, which might cause unintended bias because the majority of the patients in our study had AMD, which might degenerate over time.[21] Also, there might be intrinsic errors in converting Snellen BCVA to logMAR, which was used in our analysis.

In conclusion, we described the incidence, clinical presentation, culture status, initial treatment options, and final visual outcomes for patients developing endophthalmitis after intravitreal injection with anti-VEGF agents. Younger age and lower presenting IOP were predictive of achieving a better visual outcome at a 6-month follow-up after treatment. These findings provide significant utility to ophthalmologists who encounter patients suspected of having this devastating complication.

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **AOR** = adjusted odds ratio; **BCVA** = best-corrected visual acuity; **CF** = counting fingers; **CI** = confidence interval; **COR** = crude odds ratio; **EVS** = Endophthalmitis Vitrectomy Study; **HM** = hand motions; **IIA** = intravitreal injection of antibiotics; **IOP** = intraocular pressure; **logMAR** = logarithm of the minimum angle of resolution; **PPV** = pars plana vitrectomy; **SD** = standard deviation; **TAI** = tap and injection of intravitreal antibiotics; **VEGF** = vascular endothelial growth factor.

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