Postinjection Endophthalmitis Rates and Characteristics Following Intravitreal Bevacizumab, Ranibizumab, and Aflibercept

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• PURPOSE: To compare the incidence and clinical outcomes of endophthalmitis following intravitreal injections of bevacizumab, ranibizumab, and aflibercept.
• DESIGN: Multicenter, retrospective cohort study.
• METHODS: All included patients had received intravitreal injections of bevacizumab, ranibizumab, or aflibercept between January 1, 2009 and September 30, 2013 at 5 retina practices. Billing records were used to identify the total number of anti–vascular endothelial growth factor (VEGF) injections administered. Patients who developed endophthalmitis were ascertained from endophthalmitis logs and billing records. Chart review of these patients was performed to confirm that the endophthalmitis was related to the antecedent anti-VEGF injection. Visual outcomes, causative organisms, and clinical course were also recorded.
• RESULTS: A total of 503 890 anti-VEGF injections were included, from which 183 cases of presumed endophthalmitis were identified. The rate of endophthalmitis for bevacizumab was 0.039% (60/153 812), which was similar to ranibizumab 0.035% (109/309 722; $P = .522$) and aflibercept 0.035% (14/40 356; $P = .693$). Similarly, there was no difference in the rates between ranibizumab and aflibercept ($P = .960$). The culture-positive rate of the vitreous/aqueous tap was 38% for both bevacizumab and ranibizumab and was 43% for aflibercept. Furthermore, visual acuity remained decreased at 3 months follow-up for bevacizumab ($P = .005$), ranibizumab ($P < .001$), and aflibercept ($P = .07$) compared to vision at causative injection.
• CONCLUSIONS: Endophthalmitis following intravitreal bevacizumab, ranibizumab, and aflibercept injection appears to occur at similar rates and have comparable visual outcomes. This study suggests that the choice of anti-VEGF agent should be primarily based on efficacy and patient response rather than concern for risk of infection. (Am J Ophthalmol 2016;165:88–93. © 2016 by Elsevier Inc. All rights reserved.)

ANTI–VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) injections have become the standard of care for treating patients with neovascular age-related macular degeneration (AMD), diabetic macular edema (DME), and macular edema owing to retinal vein occlusion (RVO).[1–5] The 3 most commonly used agents are bevacizumab (Avastin; Genentech Inc, South San Francisco, California, USA), ranibizumab (Lucentis; Genentech Inc), and aflibercept (Eylea; Regeneron Inc, Tarrytown, New York, USA). Endophthalmitis is a severe potential complication following intravitreal injection and can cause significant visual loss. Fortunately, the rate of endophthalmitis is low, with reports in the literature ranging from 0.01% to 0.08%.[6–12] A recent meta-analysis of 43 articles reported an overall incidence of endophthalmitis at 0.056% following anti-VEGF injections.[13] The study found that the most commonly isolated organisms were coagulase-negative *Staphylococcus* and *Streptococcus* species.[13]

Despite the growing use of anti-VEGF agents, there is limited evidence as to the relative safety in regard to risk of endophthalmitis among the 3 commonly used anti-VEGF agents. The purpose of this multicenter study was to compare the incidence of postinjection endophthalmitis among bevacizumab, ranibizumab, and aflibercept, as well as to assess visual outcomes and causative organisms.

METHODS

THIS MULTICENTER, RETROSPECTIVE COHORT STUDY received approval from the institutional review board (IRB) at Wills Eye Hospital and central Western IRB. The participating centers in this study include: The Retina Service of Wills Eye Hospital, Mid Atlantic Retina, Philadelphia, Pennsylvania, USA; Associated Retinal Consultants at William Beaumont Hospital, Royal Oak, Michigan, USA; Retina Consultants of Houston, Houston,

AJO.com Supplemental Material available at AJO.com.

Accepted for publication Feb 22, 2016.

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0002-9394/$36.00
http://dx.doi.org/10.1016/j.ajo.2016.02.028

Texas, USA; Ophthalmic Consultants of Boston, Boston, Massachusetts, USA; and Southeastern Retina Associates, Chattanooga, Tennessee, USA. Billing records and endophthalmitis logs were used to identify patients who developed endophthalmitis following anti-VEGF injections between January 1, 2009 and September 30, 2013. The total number of injections of bevacizumab, ranibizumab, and aflibercept administered for neovascular AMD, DME, proliferative diabetic retinopathy (PDR), branch RVO with macular edema, or central RVO with macular edema was determined from billing records.

Patients' charts were subsequently reviewed to confirm that the endophthalmitis was linked to the preceding anti-VEGF injection. Furthermore, data on each patient's visual acuity (VA), indication for anti-VEGF injection, date of causative injection, anterior/vitreous chamber tap and injection of antibiotics or pars plana vitrectomy (PPV), and culture results were recorded.

• **INCLUSION AND EXCLUSION CRITERIA:** All patients diagnosed with presumed infectious endophthalmitis following an intravitreal injection of either bevacizumab, ranibizumab, or aflibercept were included in this study. Endophthalmitis was defined as patients who presented with a clinical suspicion that was high enough to warrant either a vitreous tap (or anterior chamber tap if vitreous fluid was not able to be obtained) and injection of antibiotics or PPV. In general, these patients had presented with decreased visual acuity and pain, and had signs of intraocular inflammation on examination (generally ≥2+ anterior segment cellular reaction and/or posterior segment vitritis) within 7 days of the causative injection. Furthermore, patients were only included if the indication for anti-VEGF injection was 1 of the following diagnoses: neovascular AMD, DME/PDR, or macula edema owing to branch or central RVO. Patients were excluded if they had postinjection inflammation treated with topical steroids rather than an intraocular tap with injection of antibiotics.

• **INJECTION TECHNIQUE:** All anti-VEGF injections were administered in an office-based setting. Bevacizumab was repackaged into syringes at compounding pharmacies and distributed to the participating sites. On the other hand, ranibizumab and aflibercept syringes were loaded from single-use vials during the office visit. Eyes typically received 2 cycles of topical anesthesia and 5% povidone-iodine (Betadine 5%; Alcon Labs, Fort Worth, Texas, USA). In some patients, additional 1%–2% subconjunctival lidocaine followed by 5% povidone-iodine was also administered. The use of a sterile speculum, choice of quadrant for injection, and conjunctival displacement were performed at the discretion of the treating physician. A 30 or 31 gauge needle was used to perform the injection 3.5–4.0 mm from the limbus. During the initial period of the study, patients were routinely prescribed postinjection topical antibiotics for prophylaxis. This was followed by a transition period in which some physicians continued prescribing prophylactic topical antibiotics. Finally, toward the end of the study frame, antibiotics were not routinely prescribed.

• **STATISTICAL ANALYSIS:** The primary outcome of the study was to compare the incidence of postinjection endophthalmitis among bevacizumab, ranibizumab, and aflibercept. Pearson χ^2 analysis was used to determine if there was a statistically significant difference in the rates of endophthalmitis among the 3 agents. Odds ratios (OR) were also calculated to compare the odds of developing endophthalmitis among the anti-VEGF agents. Visual acuity was converted to logarithm of the minimal angle of resolution (logMAR) values for analysis. Patients with visual acuity of counting fingers or worse were converted to logMAR units as previously described.[14] Subsequently, paired 2-tailed *t* test analysis was performed to determine visual outcomes at the time of diagnosis and at 3 months follow-up for each agent. Statistical analysis was performed using GraphPad software (GraphPad, La Jolla, California, USA).

RESULTS

A TOTAL OF 183 CASES OF ENDOPHTHALMITIS WERE IDENTIfied from 503 890 anti-VEGF injections (1/2753 injections, 0.036%). Baseline characteristics for the 3 anti-VEGF agents are summarized in Table 1. From a total of 153 812 bevacizumab injections, 60 cases (1/2563 injections, 0.039%) of endophthalmitis occurred. For patients receiving ranibizumab injections, a total of 109 cases of postinjection endophthalmitis were reported from 309 722 ranibizumab injections (1/2841 injections, 0.035%). In the aflibercept group, 14 cases of endophthalmitis were identified from a total of 40 356 injections (1/2882 injections, 0.035%). The OR of developing endophthalmitis following bevacizumab compared to ranibizumab was 1.11 (95% confidence interval [CI], 0.81–1.52; $P = .522$). The OR comparing bevacizumab to aflibercept was 1.12 (95% CI, 0.63–2.01; $P = .693$). Similarly, the OR comparing ranibizumab with aflibercept was 1.01 (95% CI, 0.58–1.77; $P = .960$).

Table 2 summarizes the microorganisms isolated from the culture-positive cases for each anti-VEGF agent. Coagulase-negative *Staphylococcus* was the most commonly isolated organism for both bevacizumab (69.6%) and ranibizumab groups (43.9%). The second most common causative organism was *Streptococcus* species, which represented 21.7% of the organisms in the bevacizumab group and 22.0% in the ranibizumab group. For the aflibercept group, the culture-positive cases were due to either coagulase-negative *Staphylococcus* (50%) or *Streptococcus* species (50%). Table 3 reports visual outcomes according to

TABLE 1. Postinjection Endophthalmitis for Bevacizumab, Ranibizumab, and Aflibercept: Baseline Demographics and Ocular Characteristics

Baseline Characteristics	Bevacizumab (n = 60)	Ranibizumab (n = 109)	Aflibercept (n = 14)
Age (y)			
Mean (SD)	75 (12.5)	80 (9.2)	82 (6.1)
Number of prior injections			
Mean (SD)	10.1 (9.6)	13.9 (11.1)	13.3 (10.8)
Mean VA at causative injection	20/110	20/91	20/107
Number of injections by diagnosis (%)			
Neovascular AMD	108 707 (70.7%)	274 209 (88.5%)	33 217 (82.3%)
Diabetic eye disease	24 702 (16.1%)	16 234 (5.3%)	46 (0.1%)
Retinal vein occlusion	20 403 (13.2%)	19 279 (6.2%)	7093 (17.6%)

AMD = age-related macular degeneration; VA = visual acuity.

TABLE 2. Postinjection Endophthalmitis for Bevacizumab, Ranibizumab, and Aflibercept: Microbiologic Spectrum

	Bevacizumab	Ranibizumab	Aflibercept
Positive culture, n (%)	23 (38%)	41 (38%)	6 (43%)
Staph. epidermidis	10	3	1
Coagulase-negative *Staph.*	4	12	1
Strep. pneumonia	3	2	1
Strep. mitis	0	4	1
Staph. aureus	0	5	0
Staph. lugdunesis	2	2	0
Strep. viridans	1	2	1
Enterococcus fecalis	1	4	0
Staph. auricularis	0	0	1
Staph. hominis	0	1	0
Strep. sanguis	0	1	0
Strep. salivarius	1	0	0
Candida parapsicolosis	0	1	0
Lactobacillus	1	0	0
Nondifferentiated gram-positive cocci	0	1	0
Propionibacterium	0	1	0
Haemophilus influenzae	0	2	0

Staph = *Staphylococcus*; *Strep* = *Streptococcus*.

TABLE 3. Postinjection Endophthalmitis for Bevacizumab, Ranibizumab, and Aflibercept: Visual Outcomes According to Culture Results

	Bevacizumab	Ranibizumab	Aflibercept
Culture-positive cases			
Mean VA (causative injection)	20/96	20/73	20/103
Mean VA (3 months)	20/455	20/968	20/1222
P value[a]	.035	<.001	.161
Culture-negative cases			
Mean VA (causative injection)	20/120	20/109	20/120
Mean VA (3 months)	20/224	20/400	20/203
P value[a]	.042	<.001	.119
Coagulase-negative *Staphylococcus* cases			
Mean VA (causative injection)	20/90	20/69	20/317
Mean VA (3 months)	20/257	20/446	20/341
P value[a]	.158	.007	.423
Streptococcus cases			
Mean VA (causative injection)	20/100	20/118	20/33
Mean VA (3 months)	CF	HM	CF
P value[a]	.149	.001	.174

CF = counting fingers; HM = hand motion; VA = visual acuity.
[a]All *P* values are compared to baseline VA, defined as VA at "causative injection."

culture results. Overall, visual outcomes were better in culture-negative cases than in culture-positive cases at 3 months follow-up for the 3 anti-VEGF agents. Furthermore, culture-positive cases due to coagulase-negative *Staphylococcus* had better visual outcomes at 3 months than those related to *Streptococcus* species for all groups.

In the bevacizumab group, patients were diagnosed with endophthalmitis after a mean of 3.9 ± 3.0 days from the causative injection. At the time of diagnosis, a tap and inject was performed in 58 cases, while 2 patients received a PPV. Nine additional cases (9/60; 15%) in the bevacizumab group underwent a PPV on average 25.2 days after the initial diagnosis. Mean logMAR VA was 0.74 ± 0.54 (Snellen equivalent: 20/110) at the time of the causative injection (baseline) and decreased to 2.27 ± 0.86 (Snellen equivalent: counting fingers, $P < .001$) at diagnosis. At 3 months follow-up, VA improved to 1.14 ± 1.04 (Snellen equivalent: 20/276, $P = .005$ compared to baseline VA).

For patients in the ranibizumab group, endophthalmitis was diagnosed on average 4.4 ± 3.7 days after the date of causative injection. A tap and inject was performed initially for 104 patients, while 5 patients received

immediate PPV. Subsequently, 16 additional patients (14.7%) underwent PPV on average 72.6 days after the initial diagnosis. Mean initial logMAR VA was 0.66 ± 0.62 (Snellen equivalent: 20/91), and decreased to 2.40 ± 0.98 (Snellen equivalent: counting fingers, $P < .001$) at diagnosis. At 3 months follow-up, VA was 1.46 ± 1.19 (Snellen equivalent: 20/576, $P < .001$ compared to baseline VA).

In the aflibercept group, patients were diagnosed with endophthalmitis on average 3.7 ± 1.9 days following the causative aflibercept injection. At the time of diagnosis, 13 patients received a tap and inject, while only 1 patient underwent PPV. Subsequently, 4 additional patients (4/14; 28.6%) underwent a PPV on average 81 days after the initial diagnosis. Mean logMAR VA at baseline was 0.75 ± 0.74 (Snellen equivalent: 20/112), and decreased to 2.03 ± 0.83 (Snellen equivalent: counting fingers, $P = .001$) at diagnosis. At 3 months follow-up, VA improved to 1.43 ± 1.16 (Snellen equivalent: 20/538, $P = .07$ compared to baseline).

DISCUSSION

THIS STUDY DEMONSTRATED THAT THE RATE OF POSTINjection endophthalmitis is similar among eyes receiving intravitreal injections of bevacizumab, ranibizumab, and aflibercept. In addition, the percentage of culture-positive endophthalmitis cases was similar among the 3 agents. Coagulase-negative *Staphylococcus* and *Streptococcus* species were the first and second most commonly isolated organisms, respectively, for patients receiving bevacizumab and ranibizumab. For the aflibercept group, coagulase-negative *Staphylococcus* (50%) and *Streptococcus* species (50%) accounted for all culture-positive cases.

Endophthalmitis rates for ranibizumab and bevacizumab were recently described from a total of 383 810 injections using the national database OptumInsight.[15] In that study, the incidence of endophthalmitis was 0.017% following 296 565 compounded bevacizumab injections and 0.025% following 87 245 ranibizumab injections ($P = .11$).[15] These findings are consistent with our study, demonstrating comparable endophthalmitis rates for bevacizumab and ranibizumab. Of note, bevacizumab is a compounded medication, whereas ranibizumab and aflibercept injections are loaded in office from single-use vials. This is particularly significant given the recent perception that compounded medications, including bevacizumab, may predispose patients to a higher risk of infection.[16]

Another recent study assessed the incidence of anti-VEGF-related endophthalmitis from a total of 121 285 injections. They demonstrated similar rates of postinjection endophthalmitis for bevacizumab (0.012%), ranibizumab (0.018%), and aflibercept (0.031%).[17] Furthermore, they report an overall culture-positive rate of 45%, which is similar to that noted in our study (38%). However, all 6 cases of endophthalmitis following aflibercept were culture-negative, whereas the culture-positive rate for aflibercept-related endophthalmitis was 43% in our study. In addition, 5 of the 6 cases in the aflibercept group of their study had a final follow-up VA that was within 1 line of their preinjection VA, while in our study VA decreased from 20/112 at baseline to 20/538 at 3 months follow-up. This supports the notion that cases of noninfectious inflammatory reactions may have been included.[17]

Sterile inflammatory reactions are uncommon but have been well described in patients receiving aflibercept injections. In a study by Goldberg and associates, the incidence of aflibercept-related sterile inflammation was 0.37%.[18] In their study, 19 of the 20 cases of inflammation eventually regained their preinjection visual acuity.[18] Similarly, Hahn and associates described 15 cases of sterile inflammation following aflibercept injection, all of which recovered visual acuity to within 1 Snellen line of their baseline.[19] It is important to recognize that differentiating between noninfectious and infectious endophthalmitis can be difficult, as they may share similar clinical features consisting of pain, conjunctival injection, and decreased visual acuity.[19]

In our study, patients were diagnosed with endophthalmitis on average 3.7, 3.9, or 4.4 days after the causative injection for the aflibercept, bevacizumab, and ranibizumab groups, respectively. At the time of diagnosis visual acuity decreased, on average, to counting fingers. Interestingly, a PPV was performed in 15% of eyes in the bevacizumab group and 14.7% of eyes in the ranibizumab group, whereas 28.6% of eyes in the aflibercept group underwent a PPV. While this difference may represent more severe infection related to aflibercept injections, it is more likely related to having a smaller sample size (14 cases), as the microbiological organisms isolated were similar to the bevacizumab and ranibizumab groups.

There are several strengths of this study. To our knowledge, this study of 503 890 anti-VEGF injections is the largest to date to evaluate anti-VEGF injection–related endophthalmitis. Furthermore, this large multicenter study consists of 5 retina practices across the United States who used several different compounding pharmacies to obtain bevacizumab. This suggests that bevacizumab was distributed in a safe manner, at least from the pharmacies used by these practices. Additionally, this study includes endophthalmitis cases following aflibercept, while other large studies have primarily focused on comparing ranibizumab and bevacizumab.

There are limitations of this study, as well. While our aflibercept group may have the largest number of injections included in a study to date, it is still considerably smaller than both the bevacizumab and ranibizumab groups. Also, the overall culture-positive rates in this study ranged from 38% to 43%, which was lower than expected. This may be partly attributed to having also included patients who received an anterior chamber paracentesis if vitreous

fluid was not sufficiently obtained. In fact, from the 43 patients that received an anterior chamber paracentesis, only 10 had a positive culture (23.3%). Another limitation is related to the retrospective nature of the study and the fact that intravitreal injection practices varied over time. For example, during the initial time frame of the study period, physicians often prescribed topical antibiotics following injections. However, emerging evidence suggested that prophylactic antibiotics may not be effective at decreasing the risk of postinjection endophthalmitis.[20–24] As such, the study includes a transition period that eventually ended with all physicians no longer prescribing antibiotics. Such a change in practice may have impacted endophthalmitis rates in the study. In addition, our multicenter study was not designed to evaluate for local risk factors that may be present. Future large single-center studies would be more suitable to determine local risk factors for the development of endophthalmitis.

In conclusion, our study demonstrated a remarkably similar incidence of endophthalmitis following bevacizumab, ranibizumab, and aflibercept. While outbreaks owing to bacterial contamination from compounded bevacizumab have been rarely reported, this study suggests that the concern for an increased risk of endophthalmitis owing to improperly compounded bevacizumab is likely unfounded. As a result, the choice of anti-VEGF agent may be primarily based on other factors, such as efficacy and cost.

FUNDING/SUPPORT: THE J. ARCH MCNAMARA MEMORIAL FUND FOR RETINA RESEARCH THROUGH WILLS EYE HOSPITAL (Philadelphia, PA) was used for central IRB approval. Financial disclosures: Jeremy D. Wolfe receives research funding from Allergan (Irvine, CA), Genentech (San Francisco, CA), and Thrombogenics (Leuven, Belgium), and is on the speaker's bureau for Allergan (Irvine, CA), Genentech (San Francisco, CA), and Thrombogenics (Leuven, Belgium). Eric Chen receives research funding from Genentech (San Francisco, CA) and Regeneron (Tarrytown, NY). Sunir J. Garg is a consultant for Deciphera (Lawrence, KS), Xoma (Berkeley, CA), and Allergan (Irvine, CA), is on the speakers bureau for Allergan (Irvine, CA), and receives grant support from Genentech (San Francisco, CA), Regeneron (Tarrytown, NY), Eyegate (Waltham, MA), Santen (Osaka, Japan), Xoma (Berkeley, CA), Lux Biosciences (Jersey City, NJ), and Centocor (Horsham, PA). Jason Hsu receives grant support from Genentech (South San Francisco, CA), Santen (Osaka, Japan), and Ophthotech (Princeton, NJ) and has served as a consultant for Ophthotech (Princeton, NJ), Optovue (Fremont, CA), and UCB (Brussels, Belgium). The following authors have no financial disclosures: Nadim Rayess, Ehsan Rahimy, Philip Storey, Chirag P. Shah, and Francis Char DeCroos. All authors attest that they meet the current ICMJE criteria for authorship.

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