Suspected Bacterial Endophthalmitis following Intravitreal Anti-VEGF Injection: Case Series and Literature Review

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Key Words

Endophthalmitis · Suspected endophthalmitis · Anti-VEGF, intravitreal

Abstract

Aim: To report an up-to-date overview of all patients reported in the literature with suspected bacterial endophthalmitis following anti-VEGF injection. Secondly, to identify specific symptoms and signs to differentiate between infectious and noninfectious endophthalmitis. **Methods:** A Pubmed search retrieved 12 retrospective case series which had included a total of 118 patients with suspected bacterial endophthalmitis after anti-VEGF injection. Data of 15 patients from the Rotterdam Eye Hospital were added. Patients were divided into three groups: those who did not receive intravitreal antibiotics (group A), patients who received intravitreal antibiotics with biopsy-negative cultures (group B) and those with biopsy-positive cultures (group C). **Results:** The median time between anti-VEGF injection and presentation with suspected bacterial endophthalmitis was 1 day in group A compared to 3 days in groups B and C. At presentation, patients of group A had a better median visual acuity (logMAR 1.0) compared to those in groups B and C (logMAR 2.1 and 2.5, respectively). **Conclusion:** This study suggests that patients presenting with a visual acuity of 20/200 (logMAR 1.0) or less and later than 24 h after injection are more likely to have bacte-

rial endophthalmitis. To prevent undertreatment in these patients, the threshold to proceed to vitreous biopsy and empirical intravitreal antibiotics should be low.

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Introduction

Until recently, bacterial endophthalmitis following intravitreal application of anti-vascular endothelial growth factor antibodies (anti-VEGF) appeared to be a relatively rare clinical situation [1, 2]. Due to the high incidence of exudative age-related macular degeneration and other indications for anti-VEGF treatment, such as diabetic macular edema, central retinal vein occlusion and branch retinal vein occlusion, anti-VEGF injections are administered with great frequency in the western world [3–5]. Current protocols for the treatment of neovascular age-related macular degeneration dictate monthly or near-monthly injections of anti-VEGF [1]. Recent retrospective case series have reported an incidence of postinjection endophthalmitis of between 0.022 and 0.16% per injection [6, 7]. This incidence approaches that of endophthalmitis following cataract surgery. However, whereas cataract surgery occurs only once per eye, patients in the treatment of macular disorders mostly require frequent anti-VEGF injections [8–10]. Differentiation between sterile (nonin-

Table 1. Summary of all patients presenting with ‘suspected endophthalmitis’ after anti-VEGF injection reported in the literature, 2008–2011

Authors, year	Number of eyes	Biopsies taken
Bakri et al. [11], 2008	4	0
Wu et al. [7], 2008	7 (from 11)	7
Fintak et al. [6], 2008	6	6
Pilli et al. [24], 2008	3	3
Wickremasinghe et al. [25], 2008	19	5
Diago et al. [23], 2009	3	3
Georgopoulos et al. [21], 2009	8	4
Klein et al. [3], 2011	15	15
Mezad-Koursh et al. [22], 2010	14	14
Ness et al. [13], 2010	11	7
Sato et al. [14], 2010	5	5
Shah et al. [26], 2011	23	23
Rotterdam Eye Hospital, 2011	15	8
Total number of eyes	133	100

fectious) and infectious endophthalmitis can be difficult and is essential to prevent delay in treatment in the latter case or unnecessary treatment in the former.

The goal of this study was to identify clinical signs and symptoms that might help distinguish sterile, postinjection inflammation from early bacterial infection based on a review of the current literature, with the addition of our own data.

Methods

Literature Search

Literature searches of the Pubmed and the Cochrane Library databases were last conducted on January 1, 2012, with no date restrictions. The Pubmed search was conducted using the following key words: ‘endophthalmitis AND (bevacizumab OR ranibizumab)’. The searches were limited to articles published in English. For the purpose of this study, ‘suspected endophthalmitis’ was defined as undue anterior chamber infiltration or vitreous inflammation after intravitreal anti-VEGF injection.

Patients were divided into three groups: patients who did not receive intravitreal antibiotics (group A), patients who received intravitreal antibiotics with biopsy-negative cultures (group B) and those with biopsy-positive cultures (group C). Visual acuity (VA) at presentation, VA at final visit and time between anti-VEGF injection and first presentation were shown in medians to compare the three groups.

Case Series from the Rotterdam Eye Hospital: Inclusion Criteria

In the Rotterdam Eye Hospital all cases of suspected endophthalmitis are registered by means of the operating theatre

patient register, lists of bacterial cultures and the hospital infection surveillance data. The intravitreal injection unit also maintains an independent register of all patients suspected of endophthalmitis after intravitreal anti-VEGF injection. These 4 databases were used to identify patients with suspected endophthalmitis after administration of intravitreal anti-VEGF agents between January 1, 2007, and July 1, 2011. The following data (when reported) was entered in a database: gender, age, treatment diagnosis, VA before presentation, VA at presentation, pain, hypopyon, biopsy or not, intravitreal antibiotics administered or not, culture results and final VA.

Statistical Analysis

Patients were divided into three groups: patients who did not receive intravitreal antibiotics (group A), patients who received intravitreal antibiotics with biopsy-negative cultures (group B) and those with biopsy-positive cultures (group C). The median values of the following variables were calculated in the three groups: VA at presentation, VA at final visit and time between anti-VEGF injection and presentation. All descriptive analyses were obtained using SPSS® version 16 (SPSS Inc., Chicago, Ill., USA).

Results

After the Pubmed search, 12 retrospective case reports were deemed relevant to our study objective (table 1). This search revealed that the anti-VEGF agents used were predominantly ranibizumab and bevacizumab. Only 1 patient in the literature received 1 injection of pegaptanib [11]. In total, treatment indications of 118 patients included neovascular age-related macular degeneration, diabetic macular edema, central retinal vein occlusion, choroidal neovascularization in angioid streaks and macular edema associated with branch retinal vein occlusion. The data set of 118 patients was updated with a retrospective case series of 15 patients with intraocular inflammation after intravitreal anti-VEGF treatment for various chorioretinal disorders in the Rotterdam Eye Hospital, giving a total of 133 patients. Thirteen patients had been injected with bevacizumab and 2 with ranibizumab.

Thirty-seven patients did not receive intravitreal antibiotics (group A), although a biopsy had been taken in 3 of these 37 patients (8%). Ninety-six patients were treated with intravitreal antibiotics; 55 (57%) of these patients showed negative culture results (group B) and 41 (43%) patients showed positive culture results.

The duration between injection and presentation was reported in 117 (88%) of 133 patients. For all 117 patients, the mean time between injection and presentation was 2.80 days (SD 2.24). The median time of presentation after anti-VEGF injection in group A was 1.0 day [interquartile range (IQR) 1.0]. Patients in group B and C had

Table 2. Median VA and median time between injection and presentation within groups A, B and C

Group (n = 133)	Median time between injection and presentation (n = 117), days	Median VA at presentation (n = 104), logMAR	Median final VA (n = 89) logMAR
Group A: IVAB- (n = 37)	1.0 (1.00)	1.0 (1.1)	0.5 (0.7)
Group B: IVAB+, biopsy negative (n = 55)	3.0 (2.0)	2.1 (1.7)	1.0 (0.7)
Group C: IVAB+, biopsy positive (n = 41)	3.0 (2.0)	2.5 (0.7)	1.4 (1.8)

Figures in parentheses indicate IQR; IVAB- = no intravitreal antibiotics given; IVAB+ = intravitreal antibiotics given.

Table 3. Pain and hypopyon within groups A, B and C

Group	Pain		Hypopyon	
	yes	no	yes	no
A: IVAB- (n = 37)	5 (13.5%)	14 (37.8%)	2 (5.4%)	31 (83.8%)
B: IVAB+, biopsy negative (n = 55)	5 (9.1%)	13 (23.6%)	11 (20.0%)	14 (25.5%)
C: IVAB+, biopsy positive (n = 41)	10 (22.7%)	5 (11.4%)	9 (20.5%)	9 (20.5%)

IVAB- = No intravitreal antibiotics given; IVAB+ = intravitreal antibiotics given.

the same median time between injection and presentation: 3.0 days with an IQR of 2.0 for both groups.

VA at presentation was reported in 104 (78%) of 133 patients. The mean VA for all 104 patients at the time of diagnosis was logMAR 1.43 (SD 0.76). Group A had a median VA of logMAR 1.0 (IQR 1.1) at presentation, whereas group B had 2.1 (IQR 1.7) and group C 2.5 (IQR 0.7). The final VA was reported in 89 (67%) of 133 patients. At their last reported visit, group A patients had a median VA of logMAR 0.5 (IQR 0.7) while those in group B had a logMAR of 1.0 (IQR 0.7) and those in group C a logMAR of 1.40 (IQR 1.8; table 2).

In 52 (39%) of 133 patients, it was noted whether the patient experienced pain or not. The highest percentage of patients with pain was found in group C (22.7%) followed by group A (15.2%) and group B (8.3%).

Hypopyon, or its absence, at presentation was noted in 76 (57%) of 133 patients. Patients in group A presented with hypopyon in 6.1% of the cases compared to 18.3 and 20.5% in groups B and C, respectively (table 3).

Of the biopsy-positive cultures (group C, n = 41), coagulase-negative *Staphylococcus* was isolated in 24 (59%) eyes. Other frequent isolates included *Streptococcus* sp. in 12 (29%), *Staphylococcus aureus* in 3 and *Propionibacterium acnes* in 2 eyes (table 4).

Table 4. Positive culture results out of 100 biopsies from 13 retrospective case series

	Number	Percent
Coagulase-negative staphylococci	24	58.5
<i>Staphylococcus aureus</i>	3	7.3
<i>Streptococcus</i> spp.	10	24.4
<i>Propionibacterium acnes</i>	2	4.9
<i>Enterococcus faecalis</i>	2	4.9
Total	41	

Discussion

Postinjection endophthalmitis differs from postoperative endophthalmitis in several respects, including time of presentation, visual outcome and presenting symptoms. Lalwani et al. [12] reported a mean time of 13 days between cataract surgery and the diagnosis of endophthalmitis. Endophthalmitis after anti-VEGF injection occurs much more quickly. Our data of 133 patients report a mean time of 2.80 days (SD 2.24) after anti-VEGF injection. An explanation for this finding may be that microorganisms present on the eyelashes, on the lid margin or

in the conjunctiva of the affected eye are directly injected into the vitreous during intravitreal injection, whereas perioperative contamination of the anterior chamber is considered to be the infection route leading to postoperative endophthalmitis.

Patients in group A did not receive intravitreal antibiotics, but the median final VA was logMAR 0.50 compared to logMAR 1.0 at presentation. This clinical improvement with only topical steroid or antibiotic eye-drops is highly suggestive of a sterile inflammation rather than a bacterial infection.

Important differences in time between injection and presentation in the three groups were noted. In group A, the median time of presentation after anti-VEGF injection was 1 day, while this was 3 days in groups B and C (table 2). VA at presentation was also markedly better in group A than in groups B and C. This would suggest that patients presenting in the first 24 h after the injection and a VA better than 20/200 are more likely to have a sterile inflammatory reaction caused by a noninfectious substance compared to patients presenting more than 1 day after injection.

Toxic inflammatory reactions have been described after intravitreal injections with bevacizumab and ranibizumab. Ness et al. [13] and Sato et al. [14] both describe inflammatory reactions after intravitreal anti-VEGF therapy in 16 patients with negative cultures. Ness et al. [13] compared this toxic inflammation after intravitreal injection with toxic anterior segment syndrome [15]. Similarities include negative Gram stains and cultures, presentation within 1 day after intervention and a favorable response to steroid therapy only. Sato et al. [14] stated that it is difficult to differentiate sterile from infectious endophthalmitis, especially in cases with severe anterior inflammation accompanied by hypopyon. Although reported in less than half of the studies of this review, the presence of a hypopyon was not a characteristic sign for bacterial endophthalmitis after anti-VEGF injection.

The frequency of hypopyon is different between postcataract endophthalmitis and endophthalmitis after anti-VEGF injection. Hypopyon is present in approximately 80% of the patients with biopsy-proven endophthalmitis after cataract surgery [12], in contrast to 20.5% in biopsy-proven endophthalmitis after anti-VEGF therapy seen in our data. An explanation may be that in endophthalmitis after anti-VEGF injection, the vitreous is the initially infected compartment, whereas the anterior chamber is contaminated first in postcataract endophthalmitis.

Comparing the functional outcome of patients with postcataract and postinjection endophthalmitis is inher-

ently flawed, because patients requiring anti-VEGF injections for macular disease are likely to have had compromised visual function even prior to the onset of endophthalmitis, whereas the functional potential in patients after cataract surgery is generally excellent. Indeed, compared to Endophthalmitis Vitrectomy Study outcomes, more than 30% of the patients with proven endophthalmitis had a VA of >20/40 [16]. On the other hand, only 11% of the patients in our review treated with intravitreal antibiotics for postinjection endophthalmitis achieved a final VA >20/40.

Pathogens cultured after endophthalmitis after anti-VEGF injection may be different from organisms frequently isolated after cataract surgery. Lalwani et al. [12] found coagulase-negative *Staphylococcus* in 50 of 73 (68.4%) eyes. Other isolates included *S. aureus* in 5 of 73 (6.8%) and *Streptococcus* sp. in 6 of 73 (8.2%). Both postcataract and postinjection infections are generally caused by contamination with resident, commensal flora of the patients' conjunctiva and eyelids, present in 80% of the general population [17, 18]. McCannel [19] stated that streptococcal isolates are approximately 3 times more frequent in cases of endophthalmitis after intravitreal anti-VEGF injection than in those after intraocular surgery. The meta-analysis conducted by McCannel included 5 reports used in ours. We also found a higher incidence of *Streptococcus* sp. in our data (29%) compared to incidences after intraocular surgery reported by Lalwani et al. [12] (8.2%) and the Endophthalmitis Vitrectomy Study [16] (9%). As *Streptococcus* sp. are generally found more frequently in mucosal biotype, the suggestion was made that not only contamination from the patient's skin and conjunctiva, but also oral or nasal contamination from the patient or injecting professionals might be a factor in postinjection endophthalmitis [20]. This might form the basis of a recommendation for stricter hygienic precautions, including sterile draping of the patient and the use of a surgical mask by all health care professionals in the injection room.

The present study has several weaknesses: all data were collected from retrospective case series which had neither uniform inclusion criteria nor uniform protocols dictating the conditions under which the clinician should proceed to vitreous biopsy and intravitreal antibiotics. Nor did these studies have uniform entry and outcome data. However, considering the fairly recent increase in the incidence of infection after intravitreal injection, and the lack of prospective studies, the present study may be of value in identifying patients most at risk for infectious endophthalmitis based on specific signs and symptoms.

In our review of retrospective studies, VA and time between injection and presentation were the only regularly reported signs. The data of this present review do not allow us to calculate a cutoff point in VA that safely separates sterile from infectious endophthalmitis after anti-VEGF injection. However, we emphasize that in patients presenting 24 h or more after injection with a presenting VA of 20/200 (logMAR 1.0) or less the likelihood of sterile endophthalmitis is small. In these patients the threshold to proceed to vitreous biopsy and empirical intravitreal antibiotics should be accessible. Patients that do not (yet) meet these criteria should ideally be observed close-

ly at short intervals. Continued monitoring of the side effects of intravitreal anti-VEGF therapy is essential for early recognition and adequate treatment of both noninfectious and infectious endophthalmitis. For this monitoring, accurate registration and standardization of the signs and symptoms in patients with suspected endophthalmitis are critical.

Disclosure Statement

The authors state no conflict of interest.

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