Incidence and management of acute endophthalmitis after intravitreal bevacizumab (Avastin) injection

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CLINICAL STUDY

Abstract

Introduction The aim of this study was to report the incidence and management of acute endophthalmitis after intravitreal injection of Avastin (bevacizumab), and visual acuity outcomes of three eyes of three patients who developed acute endophthalmitis following intravitreal injection of Avastin.

Methods This clinical retrospective, non-comparative study included 3022 intravitreal injections of 1.25 mg bevacizumab consecutively performed for 1822 eyes with exudative age-related macular degeneration and other retinal diseases. Of 3022 injections, 1200 were reinjections. After clinical appearance of post-injection endophthalmitis, immediate intervention was performed, including injection of intravitreal antibiotics and early pars plana vitrectomy.

Results Three eyes of three patients with acute postoperative endophthalmitis were identified in the first week following intravitreal injections of 1.25 mg bevacizumab. Among of these patients, two cases were culture-positive and one case was culture-negative. Compared with presenting visual acuities, all of three patients improved at the end of follow-up time. The overall incidence rate of post-injection culture-proven endophthalmitis was 0.066%.

Discussion Acute culture-proven endophthalmitis is still a potential complication of intravitreal bevacizumab injection (approximately 0.066%) despite using maximal sterile techniques. Acute post-injection endophthalmitis following intravitreal bevacizumab occurs rapidly and can result in severe loss of vision. Prompt

recognition and treatment are key in maximizing outcomes in patients who developed endophthalmitis after intravitreal injection of bevacizumab.

Eye (2009) 23, 2187–2193; doi:10.1038/eye.2009.7; published online 13 February 2009

Keywords: intravitreal injection; bevacizumab; endophthalmitis

Introduction

Intravitreal injection of medications is becoming increasingly accepted for treatment of various retinal disorders, with effective intravitreal therapies being commonly administered in the vitreoretinal clinical or surgical environment. With the increase in use of these agents, the risk of endophthalmitis is becoming an important concern. Off-label intravitreal injections of bevacizumab (Avastin; Genentech Inc., South San Francisco, CA, USA) have been given for the treatment of neovascular and exudative ocular diseases since May 2005.^{1,2} Since then, the use of intravitreal bevacizumab (IVB) has spread worldwide, but the drug-related adverse events associated with its use have been reported in a few retrospective reviews. IVB is increasingly being used for the treatment of ocular diseases. However, the treatment is not without risks. None of the adverse event rates exceeded 0.21%.³ Endophthalmitis is a serious intraocular inflammatory disorder resulting from infection of the vitreous cavity. Exogenous endophthalmitis occurs when infecting organisms gain entry into the eye by direct inoculation through intraocular surgery, penetrating trauma, or intravitreal injection.⁴ The risk of endophthalmitis after intravitreal

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Received: 19 November 2008

Accepted in revised form: 5 January 2009

Published online: 13 February 2009

All the authors have no proprietary interest in any products or concepts mentioned in this article.

injection may vary among agents that are employed.⁵ The reported incidence of endophthalmitis per patient in multi-centre clinical trials with anti-vascular endothelial growth factor (VEGF) therapy ranged from 0.019 to 1.6%.^{6–8} Although cases of acute endophthalmitis following IVB have occurred, the exact incidence rate remains unknown. Concerns have been raised regarding injection technique and also about the use of bevacizumab because of compounding issues. Generalized categories that lump adverse events are less useful than a clear statement of the rate of individual, clinically relevant endophthalmitis. Treating physician wants to know the specific rates of endophthalmitis and its management. The purpose of our study was to report the incidence rates of culture-positive and culture-negative endophthalmitis for patients receiving IVB. The current study also includes the clinical findings, causative organisms, management, and visual acuity outcomes of three eyes of three patients who developed acute postoperative endophthalmitis after IVB injection.

Materials and methods

This is a retrospective, interventional case series of 3022 consecutive eyes that were administered IVB injection at our reference clinic for miscellaneous retinal disease, which was presented after March 2005. The indications for injection included predominately exudative age-related macular degeneration (AMD; $n = 1453$), choroidal neovascular membranes secondary to myopic degeneration ($n = 21$), idiopathic, and other secondary causes ($n = 18$); cystoid or diffuse macular oedema from central and branch vein occlusions, diabetes, uveitis and retinitis pigmentosa ($n = 310$); and proliferative retinopathies ($n = 20$). All patients included in the study were identified using comprehensive billing records. A search of the office database was conducted for endophthalmitis diagnosis codes and intravitreal injection procedure codes to identify all patients having IVB and those who developed endophthalmitis. Patients were included in the study if they had clinical evidence of acute postoperative endophthalmitis after receiving an IVB injection. Acute postoperative endophthalmitis was defined as the presence of progressive inflammation in the vitreous cavity (vitritis) and/or anterior chamber (iritis) within 4 weeks following intravitreal injections of bevacizumab. Culture-positive endophthalmitis was considered to be present if the patient had either a positive gram stain or a positive culture. If the fungal, aerobic, and anaerobic culture were all negative, then this case was accepted as culture-negative endophthalmitis. Common clinical findings were hypopyon, pain, red eye, and decreased vision. Informed consents were obtained from all participants after thorough discussion and full

understanding on the potential benefits and risks of IVB treatment and other alternative treatment modalities. The study protocol was complied with the provisions of the Declaration of Helsinki Principles and was reviewed and approved by the ethics committee. Patients were excluded from the study if the bevacizumab was used as part of another surgical procedure (ie cataract surgery, pars plana vitrectomy (PPV), air–fluid exchange). Eyes were also excluded from the study if another intraocular procedure was performed at least 4 weeks before injection.

IVB injection was performed as an outpatient procedure under strict aseptic technique. Local anaesthesia was achieved using 0.5% proparacaine (Alcaine; Alcon Laboratories Inc., Fort Worth, TX, USA) and 10% povidone-iodine solution was applied to the eyelids and in the conjunctival sac for 5 min, followed by draping and insertion of a lid speculum. Intravitreal injection of 1.25 mg bevacizumab in 0.05 ml was then carried out using a separate, sterile 30-gauge needle at 4-mm post-limbus in the inferior or inferotemporal quadrant. The needle was removed simultaneously with the application of a cotton tip over the entry site. Immediately after injection, 10% povidone-iodine solution was applied on the ocular surface. Bevacizumab (100 mg/4 ml; Roche; Genentech Inc.) was kept refrigerated at 4°C in its 4 ml original vial, and the studied volume of 0.05 ml was directly withdrawn from the vial just before each injection. Ten patients were grouped together for treatment to provide multiple doses from a single vial. The top of the container was cleaned with alcohol wipe before injection. Any unused drug was discarded after the vial had been opened for 4 h to prevent drug contamination. The optic nerve head was then examined for arterial pulsation to look for complications, and indirect ophthalmoscopy was performed to ensure correct placement of the injection and to evaluate the retina. Tonometry was carried out after the procedure. Patients were given topical ofloxacin (Exocin; Allergan Pharmaceuticals Ltd, Westport, Ireland) 3 mg/ml q.i.d. (four times a day) for 1 week after each injection. Following the injection, the patients were educated about symptoms of endophthalmitis.

At baseline and during the follow-up period, patients received a comprehensive ophthalmic examination. Post-injection examinations were scheduled between 1 and 7 days, 4 weeks, and 8 weeks.

Results

A total of 3022 intravitreal injections of bevacizumab were performed for 1822 eyes with exudative AMD and other exudative, proliferative retinal diseases during this time period. Of 3022 injections, 1200 were reinjections.

Follow-up after each injection was at least 6 weeks. Three patients were identified with signs and symptoms of acute, post-injection endophthalmitis after their first injection (Table 1). Two patients were women, and two cases involved the right eye. Indications for injections of IVB treatment included choroidal neovascular membrane associated with AMD (cases 1 and 2), and proliferative diabetic retinopathy (case 3). The study involved 274 diabetes patients. The patients with AMD were pseudophakic and those with diabetes were phakic. For cases 1, 2, and 3, the pre-injection visual acuity was 20/100, 20/200, and 20/250, respectively; the endophthalmitis presenting visual acuity was 20/400, 20/800, and 20/800, respectively; and the time to presentation after injections was 5, 4, and 3 days, respectively. Potential predisposing risk factors included non-insulin-dependent diabetes mellitus (case 3), old age (case 2, 86 years old), and blepharitis (cases 1 and 2). All of three patients have had common clinical findings, including pain, iritis, vitritis, hypopyon, red eye, and decreased and blurry vision. In all patients, ocular and orbital ultrasonography was performed and showed that no retinal detachment had occurred and no obvious extraocular inflammation was present. The patients were taken to the operation room and underwent intravitreal tap and the intravitreal injection of vancomycin (1 mg/0.1 ml) against Gram-positive bacteria and amikacin (400 µg/0.1 ml) or ceftazidime (2.25 mg/0.1 ml) against Gram-negative bacteria were performed. Furthermore, administration of hourly topical 0.5% moxifloxacin (Vigamox; Alcon Laboratories Inc.) and prednisolone acetate 1% solution was started as empirical therapy. Gram stain, Giemsa stain, acid-fast stain, acridine orange, calcofluor white, and silver stain were performed on vitreous sample. The fungal, aerobic, and anaerobic cultures were also performed on the sample for growth. The vitreous fibrin and number of cells increased and the visions decreased in all patients after 48 h. We preferred to perform early PPV instead of additional injection of intravitreal antibiotics or any systemic medication because of their progressive visual

loss. Orbital ultrasonograms before PPV showed dense vitreous opacities, vitreous membrane formation, and partial posterior vitreous detachment in all patients. The pre-vitreectomy visual acuity for cases 1, 2, and 3 was 20/800, 20/20 000, and 20/2000, respectively (Table 1). A vitreous sample of 0.2–0.5 ml is first obtained for the control culture without infusion using gentle manual aspiration into a syringe with a high cutting rate. Infusion is then initiated and core vitrectomy was performed. After core vitrectomy, intravitreal antibiotics were administered by means of sclerostomy. IOL was not removed. Postoperatively, hourly topical 0.5% moxifloxacin and prednisolone acetate 1% solution q.i.d. was continued for 2 weeks. There were no ocular and systemic complications about intravitreal antibiotics and topical therapy during the study period. Intraocular cultures were obtained in two patients: *Staphylococcus epidermidis* (case 3) and *Haemophilus influenzae* (case 2). *H. influenzae* and *S. epidermidis* were grown on each sample (tap and vitrectomy) separately. The fungal, aerobic, and anaerobic cultures were all negative in one patient (case 1; Table 1). In the 8 weeks following IVB injections, there were two cases of acute culture-positive endophthalmitis per 3022 eyes. The incidence of acute culture-positive endophthalmitis was 0.066%. The post-infection vision for cases 1, 2, and 3 at the end of follow-up time improved to 20/200, 20/250, and 20/200, respectively. All of three patients demonstrated an improvement in visual acuity from presentation of endophthalmitis. Compared with pre-treatment visual acuities, vision at 2 months and at the last follow-up examination was stable in three eyes: one patient improved (case 3), and two patients (cases 1 and 2) had minimal visual loss (Table 1).

Conclusion

Endophthalmitis is a serious, potentially vision-threatening condition that can be present in various settings. Acute postoperative endophthalmitis refers to infectious endophthalmitis that occurs shortly after ocular surgery or

Table 1 Clinical characteristics, visual measurements, interventions, cultures, and follow-up time of three patients with endophthalmitis after intravitreal injection of Avastin

Cases	Sex	Eye	Presentation time	Age	Indication	Pre-VA	Present-VA	Pre-PPV-VA	Post-VA	P. intervention	Culture	Follow-up
1	F	L	5 days	69	CNV	20/100	20/400	20/800	20/200	T + I, PPV	Negative	8 weeks
2	M	R	4 days	86	CNV	20/200	20/800	20/20 000	20/250	T + I, PPV	<i>Haemophilus influenzae</i>	6 weeks
3	F	L	3 days	64	PDR	20/250	20/800	20/2000	20/200	T + I, PPV	<i>Staphylococcus epidermidis</i>	7 weeks

F, female; M, male; L, left eye; R, right eye; CNV, choroidal neovascularization; PDR, proliferative diabetic retinopathy; pre-VA, best-recorded visual acuity before intravitreal bevacizumab injection; present-VA, best-recorded visual acuity at the time of presenting with endophthalmitis; pre-PPV-VA, best-recorded visual acuity before pars plana vitrectomy (20/2000 is equivalent to counting fingers at 2 feet; 20/20 000 is equivalent to hand motion at 2 feet); post-VA, best visual acuity post-infection at the end of follow-up time; PPV, pars plana vitrectomy; P. intervention, primary intervention; T + I, vitreous tap with injection of intravitreal antibiotics; culture, microbiology culture results.

intravitreal injection of medications.⁴ Newer therapies such as IVB used to treat retinal diseases involve increased injections of medications directly into the vitreous. The intravitreal approach increases the potential introduction of bacteria into the eye and the subsequent development of endophthalmitis. Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that inhibits human VEGF.^{1–2} It has been administered off-label, intravitreally in VEGF-mediated diseases, such as choroidal neovascularization,⁶ central retinal vein occlusion, proliferative diabetic retinopathy, and pseudophakic cystoid macular oedema.⁹ Although there are no long-term safety studies in humans, limited human and animal studies show that IVB seems to be safe.^{10,11}

Although it is difficult to compare data regarding endophthalmitis associated with different types of intravitreal injections, the published meta-analysis by Jager *et al*¹² shows that it seems the prevalence is low. The authors evaluated the incidence of endophthalmitis following intravitreal injections and separated them into two categories: infectious and noninfectious endophthalmitis. They found that the endophthalmitis rate was 0.9% (38/4382) per eye and 0.3% (38/14 866) per injection, when looking at both infectious and noninfectious cases. In the same review, an estimated rate of endophthalmitis was 1.4% per injection for intravitreal triamcinolone acetonide and 0.2% per injection for intravitreal ranibizumab. Jonas *et al*¹³ reported that the rate of infectious endophthalmitis after an intravitreal injection of 1.5 mg bevacizumab was 1:1000. Aggio *et al*¹⁴ also reported two cases of acute endophthalmitis following IVB injection. In the VEGF Inhibition Study in Ocular Neovascularization (VISION) clinical trial, 890 patients with neovascular AMD received intravitreal injections of pegaptanib every 6 weeks over a study period of 54 weeks. Twelve patients developed endophthalmitis (1.3%), and the per injection endophthalmitis rate was calculated to be 0.16%.¹⁵ Many of the infections in the VISION study were attributed to protocol violations, chief of which was not using a lid speculum. Also, the needle size for pegaptanib was 27 gauge, which is larger than that used for other anti-VEGF agents. A change in protocol in the VISION study reduced the apparent incidence of endophthalmitis. Another randomized control trial investigated the use of pegaptanib in the treatment of diabetic macular oedema and found the endophthalmitis occurrence rate to be 0.8% per subject and 0.15% per injection.¹⁶ Ranibizumab, an antibody fragment targeting all active isoforms of VEGF-A, recently reported the safety profile in a phase 1 multi-centre, controlled, multi-dose study. Endophthalmitis occurrence rates in this study were 1.6% per subject and 0.25% per injection.¹⁷ In the MARINA study, the incidence of endophthalmitis was 0.05% per

injection (5 cases/10 443 injections).⁷ In the ANCHOR trial, two patients were classified as having suspected or proven endophthalmitis in the 0.5 mg group, but the total number of injections was not reported.⁸ In a recent Internet-based survey to assess drug safety, Fung *et al*³ found the infectious endophthalmitis rate after IVB to be 0.01%. In one retrospective analysis for anti-VEGF therapy (including 406 pegaptanib, 6347 ranibizumab, and 3501 bevacizumab injections), the incidence of suspected endophthalmitis per injection was given very low, 0.029%, with no culture-positive endophthalmitis.¹⁸ In this study, pre-injection antibiotics and eyelid speculum were not used within the procedure. Mason *et al*¹⁹ reported only one case among 5233 consecutive IVB injections. In that study, the decision whether to use pre-injection and/or post-injection antibiotics, as well as whether to place a lid speculum, was made at the discretion of each treating physician. Approximately 50% of injections were performed with use of a lid speculum and approximately 50% of patients used post-injection gatifloxacin. We uniformly used a lid speculum, povidone-iodine prophylaxis, 30-gauge needle, and post-injection antibiotics for preventing infection. In our study, we have evaluated incidence of culture-proven infectious acute endophthalmitis of 0.066% per injection in the first 6 weeks following intravitreal injection of 1.25 mg bevacizumab despite strict aseptic technique.

Clinical characteristics that may have increased the risk of endophthalmitis included insulin-dependent diabetes mellitus, old age, and blepharitis. Diabetes mellitus and old age have also been associated with immunosuppression and an increased susceptibility to infection.^{20–22} This susceptibility may increase the risk of endophthalmitis in diabetic and elderly patients following an intravitreal injection. Numerous studies indicate that the most common source of bacteria appears to be from the patients' own flora.^{18–21} Blepharitis is a reported risk factor for endophthalmitis,^{19–22} and the risk may be increased during an office-based procedure where the sterile technique may not be as rigorous as in the operating room setting. Despite disinfection of the lids and conjunctival surface with povidone-iodine, the lashes may serve as a nidus of infection if they abut the needle before its entry into the eye. Given that the source of causative bacteria is often the patient's own ocular surface or adnexa, it is reasonable to try to reduce the exposure to the injection site and injection needle. For this purpose, lid speculum used is conformable to reason. The care should be taken in all cases to ensure that the needle did not touch the lids or lashes. Vitreous wick in sclerostomy after procedure may also serve as a nidus of infection. Thus, eyelid speculum and prophylactic topical broad-spectrum antibiotics should

be used after procedure. The sclerostomy may be made oblique to prevent vitreous wick.

Bacteria are the most common infecting agents and fungi or viruses are very small part of postoperative endophthalmitis.⁴ Thus, the main treatment of postoperative acute virulent bacterial endophthalmitis is injection of intravitreal antibiotics.^{21–25} Intravitreal injection provides the quickest way to deliver adequate concentration directly to the infected tissues. Therapy should cover Gram-positive organisms, which comprised 94% of all organisms isolated in the Endophthalmitis Vitrectomy Study (EVS).²¹ Gram-negative coverage is also important.^{25–30} Our recommendation for initial empirical therapy is intravitreal injection of vancomycin 1.0 mg/0.1 ml and ceftazidime 2.25 mg/0.1 ml. In one study, sensitivities of Gram-positive bacteria to vancomycin and Gram-negative bacteria to ceftazidime remain at 99 and 100%, respectively.^{4,28} Vancomycin also provides good cover for MRSA (methicillin-resistant *S. aureus*). Ceftazidime and amikacin are used to cover the Gram-negative bacteria including *Pseudomonas aeruginosa*. Amikacin is also used for β -lactamase-positive bacteria. Reinjection should be considered if the infection fails to stabilize or improve more than 48 h after the first injection.^{2,4,21} In our study, instead of reinjection, PPV was performed. Additional injection of intravitreal antibiotics did not need to be used after PPV.

PPV has several potential benefits for acute postoperative endophthalmitis, including reduction of infecting organisms, toxins, inflammatory materials, and opacities.^{2,31,32} PPV also allows collection of samples for culture and potential improvement of intravitreal antibiotic distribution.^{2,4} The EVS addressed the relative efficacy of immediate PPV *vs* vitreous tap in treatment of postoperative endophthalmitis.²¹ According to EVS, endophthalmitis patients who presented with light perception only visual acuity had a significant, threefold improved chance of obtaining 20/40 vision after immediate PPV (33%) compared to vitreous tap or biopsy (11%). We stress that early PPV was beneficial for patients with endophthalmitis following intravitreal injection of bevacizumab. We did not wait for PPV until visual acuity fall down to light perception. Systemic therapies are usually too slow to enter the eye in adequate concentrations so we have not used these as a sole treatment for acute endophthalmitis.

In case of severe ocular infectious disease such as endophthalmitis, commercially available preparations of ophthalmic antibiotics should contain a sufficient concentration of drug to yield optimal antibacterial activity (especially for MRSA and *P. aeruginosa*) in the aqueous humour following topical administration.^{33,34} Topical fourth-generation fluoroquinolone, which contains no preservative in its commercial preparation,

was tested and found to prevent endophthalmitis successfully in recent studies.^{35–39} Moxifloxacin is a fourth-generation fluoroquinolone antibiotic agent that provides broader spectrum antimicrobial action and enhanced activity against Gram-positive bacteria, including *S. aureus* and *S. epidermidis*.^{35,36} Kowalski et al⁴⁰ suggest that topical 0.5% moxifloxacin may aid in the prevention of endophthalmitis following intravitreal injection by the elimination of commonest bacterial pathogens causing endophthalmitis at the injection site. Povidone-iodine reduces the topical ocular flora but does not penetrate the tissue for any additional antibacterial protection. Although definitive evidence does not exist to show that pre-injection and/or post-injection topical antibiotic drops reduce the incidence of endophthalmitis, enhanced topical antibiotics concentration can facilitate antibiotic bioavailability in ocular tissues (aqueous humour, vitreous humour) and improve antibacterial efficacy. We believe that pre-injection and/or post-injection administration of topical fourth-generation fluoroquinolone antibiotics decreases the number of bacteria that can be cultured from the conjunctival surface, even if the patient has been given povidone-iodine.

In our study, one patient who had culture-negative endophthalmitis had no laboratory growth. Failure to obtain positive cultures may be a result of low microbial counts, technical problems from organisms such as *Propionibacterium acnes*, which are difficult to culture, or aggressive antibiotic regimen before the culture.³³ Some bacteria, such as *S. epidermidis*, may also sterilize spontaneously during the ocular inflammatory response.³⁴ Nonetheless this case may be sterile endophthalmitis.

This study has some obvious shortcomings. It is a retrospective, uncontrolled analysis and no randomized comparison of either injection technique or medication used was performed. In spite of these limitations, these investigations indicated that although culture-positive acute infectious endophthalmitis seems to be a still potential complication of IVB injection (0.066%), IVB injection is acceptable as safe procedure. Prophylaxis of endophthalmitis with topical povidone-iodine, using drape and adherence to aseptic technique, minimizes the risk of post-injection infection. We recommend that only single-use bottles be utilized for any intravitreal injection. After administration of IVB, topical fourth-generation fluoroquinolone as a broad-spectrum antimicrobial therapy may be chosen based on the spectrum of micro-organisms most likely to be encountered under the clinical circumstances. Furthermore, the oblique sclerostomy may be helpful for the protection of vitreous wick as a potential nidus of bacterial inoculation. This study also showed that early PPV was beneficial for

patients with endophthalmitis following IVB injection independent of visual impairment. We suggest that prompt recognition and treatment including initial intravitreal antibiotic administration, early PPV, maintenance therapy with topical fourth-generation fluoroquinolone antibiotics are key in maximizing outcomes in patient with endophthalmitis after IVB. Specialist also should be aware of post-injection endophthalmitis in aged and diabetes patients.

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