

Multicenter Study of Infectious and Noninfectious Endophthalmitis after Intravitreal Ranibizumab Injections

Keywords: Age-related macular degeneration; Anti-VEGF drugs; Endophthalmitis; Intravitreal injection adverse-effects; Ranibizumab

Abstract

Study background: The purpose of this study is to evaluate the overall incidence of infectious and non infectious endophthalmitis associated with intravitreal ranibizumab (IVR) injections.

Methods: This is a retrospective, consecutive, multicenter case series involving six large clinical sites. The number of injections was determined from the injection log books and billing records. Cases of clinical diagnoses of endophthalmitis or suspected endophthalmitis resulting from IVR injection were identified and reviewed. From these data, the risk per injection was estimated.

Results: A total of 7,178 IVR injections were administered on 1,372 patients from January 1, 2007 to July 31, 2010. In this series, the incidence of clinically-suspected and culture-positive infectious endophthalmitis was 3 cases for total number of 7,178 IVR injections (0.042%), whereas the incidence of clinically-suspected and culture-negative infectious endophthalmitis was only 1 case (0.014%), and the incidence of sterile noninfectious endophthalmitis was also 1 case (0.014%). The clinical course was favorable in all patients. Posteriorly, three of the patients received other IVR injections with no complications.

Conclusions: The rate of culture-proven endophthalmitis associated with IVR injections is low, with an incidence of approximately 1 in 2,392 injections. The prognosis is good and patients with this complication do well, typically with a return to baseline vision.

Introduction

The intravitreal use of anti-vascular endothelial growth factor (anti-VEGF) agents has become the standard of care for the treatment of neovascular age-related macular degeneration (AMD). In particular, intravitreal ranibizumab (IVR) has been demonstrated to be very efficacious in different well-designed clinical trials [1,2]. It is also increasingly being used to treat other types of choroidal neovascularization (CNV) and macular edema of various etiologies [3-9]. Additionally, patients often require multiple periodic reinjections to achieve or maintain a therapeutic effect. Given both the widespread use of IVR and the potential need for frequent reinjections, the safety of these injections continues to be scrutinized.

Ranibizumab (Lucentis, Genentech Inc., South San Francisco, CA) is a fragment of a humanized, monoclonal antibody that binds to all VEGF-A isoforms, thereby, inhibiting angiogenesis and reducing vascular permeability [10]. It was specifically designed for ophthalmic use and was approved by the U.S. Food and Drug Administration for the treatment of wet AMD in June 2006. It has also shown great



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efficacy in the management of macular edema attributable to a variety of causes [1,2].

Endophthalmitis is the most feared complication of intravitreal injection of anti-VEGF drugs in general [1,11,12] and in particular ranibizumab [13,14]. Postinjection inflammation may represent culture-positive infectious endophthalmitis, culture-negative infectious endophthalmitis, or sterile noninfectious inflammation [15]. Culture-positive infectious endophthalmitis produces a potential loss of vision, which can be permanent in spite of prompt and appropriate management. The reported incidence of culture-positive infectious endophthalmitis is 0% to 0.007% after IVR injection [1,11]. Some cases of culture-negative endophthalmitis are truly infectious, but the inciting organism may be too difficult to grow in culture, and some cases are treated empirically with intravitreal antibiotics without performing a culture to prove an infectious etiology [1,13]. Other cases of culture-negative endophthalmitis resolve without intravitreal antibiotics and represent sterile noninfectious inflammation; the reported incidence of these cases for IVR injections is 0.02% to 0.07% [1,16]. The aim of the present multicenter study was to evaluate outcomes of endophthalmitis after IVR injection.

Material and Methods

This study was a multicenter, retrospective, nonrandomized interventional consecutive case series. Inclusion criteria incorporated all patients underwent IVR injections in the Departments of Ophthalmology at Bellvitge University Hospital (Barcelona, Spain), "Son Dureta" University Hospital (Palma de Mallorca, Spain), "Lozano Blesa" University Clinic Hospital (Zaragoza, Spain), "Ramon y Cajal" University Hospital (Madrid, Spain), University Clinic of Navarra (Pamplona, Spain), and "Virgen Macarena" University Hospital (Sevilla, Spain) from January 1, 2007 to July 31, 2010. The study and data accumulation were performed with the approval of the

local ethics committee of each hospital. Injections were recorded in nursing log books and these were later reviewed to assess total number of injections of this vascular targeting agent. Clinical indications for injection included: neovascular AMD, myopic CNV, and macular edema associated with various conditions. All participating patients gave informed consent. We obtained Institutional Review Board approval before initiating the study at each institution.

Patients were treated with IVR injections (0.5 mg/0.05 mL) in the surgery room under sterile conditions following the protocol for intravitreal injections of the Vitreous-Retina Spanish Society (SERV). The surface of the eye was anesthetized by applying a commercial preparation containing tetracaine and oxybuprocaine (“Colircusi Anestésico Doble,” Laboratorios Alcon, El Masnou, Spain). High-viscosity preserved tetracaine hydrochloride 0.5% (Cynacon/Ocusoft, Rosenberg, Texas, USA) drops were instilled and were left on the surface of the eyes for approximately 5 minutes. The eyelids and eyelashes were prepared with 10% povidone-iodine. The ocular surface was disinfected with 5% povidone-iodine from single-use dispensers into each conjunctiva. We used a sterile wire lid speculum, sterile gloves, and a surgical drape. Attention was paid not to touch the tip of any instruments. The injection was performed in the inferior temporal quadrant 3.5 mm to 4.0 mm posterior to the limbus with a 30-gauge needle. The needle was withdrawn from the eye, the injection site was compressed with a cotton swab to avoid reflux, and additional drops of tobramycin and 5% povidone-iodine were placed. The patients were given a bottle of tobramycin eye drops at no charge to use four times per day for four days following the injection. They were encouraged to call us if they had any problems. All patients

were rigorously evaluated before the procedure and follow-up examinations were carried out every 4 weeks.

Suspected endophthalmitis was defined as an intraocular inflammation of any amount leading to sufficient suspicion of infection that the patient was given intravitreal antibiotics with a vitreous tap or systemic antibiotics. Signs of infection included marked fibrin, intraocular inflammation, pain, and/or significant vision loss presenting within a few days of injection. Cases of post-injection uveitis that were not clinically suspected of infection were excluded. A vitreous specimen of the suspected cases was sent to the Microbiology laboratory of each hospital for gram stain, fungal, aerobic and anaerobic cultures. Proven endophthalmitis was considered to be present if the patient had either a positive gram stain or culture.

Results

A total of 7,178 IVR injections were administered on 1,372 patients from January 1, 2007 until July 31, 2010. The average number of injections per patient per eye was 5.2, with a median number of 2 and a range of 1 to 16 injections per patient. The mean time of postinjection follow-up was 39 days. Analysis of all injections documented only five reported cases of clinically-suspected endophthalmitis following injection with ranibizumab (Table 1).

In this series, the incidence of clinically-suspected and culture-positive infectious endophthalmitis was 3 cases for total number of 7,178 IVR injections (0.042%), whereas the incidence of clinically-

Table 1: Main data of patients suffering endophthalmitis following intravitreal ranibizumab injection.

| Case no. | 1 | 2 | 3 | 4 | 5 |
|----------------------|--------------------------------------|---------------------------------------|---------------------------------------|--------------------------------------|--------------------------------------|
| Sex | F | M | M | F | F |
| Age (years) | 65 | 68 | 61 | 77 | 65 |
| Diagnosis | AMD | AMD | AMD | AMD | AMD |
| Location | Juxtafoveal CNV | Juxtafoveal CNV | Subfoveal CNV | Subfoveal CNV | Juxtafoveal CNV |
| Injection no. | 3 rd | 4 th | 2 nd | 1 st | 3 rd |
| Days after injection | 3 | 2 | 2 | 5 | 3 |
| Visual acuity loss | + | + | + | + | + |
| Ocular pain | + | + | - | + | + |
| Red eye | + | + | + | + | + |
| Hypopyon | + | + | + | + | + |
| Vitritis | + | + | + | + | + |
| Vitreous culture | S. epidermidis | S. aureus | (-) | Neisseria sp | (-) |
| Treatment | Intravitreal antibiotics | Intravitreal antibiotics + vitrectomy | Periocular corticosteroids | Intravitreal antibiotics | Intravitreal antibiotics |
| Diagnosis | Culture + infectious endophthalmitis | Culture + infectious endophthalmitis | Sterile noninfectious endophthalmitis | Culture + infectious endophthalmitis | Culture - infectious endophthalmitis |
| Baseline | | | | | |
| BCVA | HM | CF | LP | HM | CF |
| Post-treatment | | | | | |
| BCVA | 1 week (20/32) | 2 weeks (20/60) | 1 week (20/100) | 3 week (20/100) | 2 weeks (20/40) |

F: Female; M: Male; AMD: Age-related Macular Degeneration; CNV: Choroidal Neovascularization; BCVA: Best-Corrected Visual Acuity; HM: Hand Motion; CF: Counting Fingers; LP: Light Perception

suspected and culture-negative infectious endophthalmitis was only 1 case (0.014%), and the incidence of sterile noninfectious endophthalmitis was also 1 case (0.014%).

Discussion

Today, antiangiogenic therapy is the standard treatment for CNV secondary to AMD. In particular, IVR injections have been demonstrated to be very efficacious in different well-designed clinical trials [1,2]. Likewise, they are also increasingly employed to treat other types of CNV and macular edema of various etiologies [3-9].

The risk of endophthalmitis after IVR injection is low. However, it must be explained to the patient and assumed before starting treatment. In MARINA study, presumed endophthalmitis occurred in five of 477 patients (rate per patient of 1%) who received a total of 10,443 IVR injections (rate per injection of 0.05%) [1]. In the ANCHOR study, during the first 12 months [2], presumed endophthalmitis occurred in two (1.4%) patients receiving ranibizumab 0.5 mg, one of whom had serious uveitis treated with antibiotics. In the PIER study, patients received ranibizumab 0.3 or 0.5 mg or a sham injection at monthly intervals for 3 months, followed by fixed quarterly dosing [17]. This regimen was generally well tolerated and there were no reported cases of endophthalmitis or serious uveitis. Pilli et al. [13], among 6,347 ranibizumab injections, found two cases of suspected endophthalmitis (rate per injection of 0.031%); these cases could not be culture-proven and both patients regained their preinjection visual acuity. Fintak et al. [11] reported three infectious endophthalmitis after administration of a total of 14,320 injections of IVR. Two of these patients were culture positive. The rate of endophthalmitis associated with IVR was low, with an incidence of approximately 1 in 4,500 injections (0.02%). In the 1-year safety results from SAILOR study [18], where 2,378 patients each received an average number of injections of 4.6, the incidence of ocular inflammation classified as adverse events (including iritis, uveitis, vitritis and iridocyclitis) was 1.0 and 1.5% for the 0.3 and 0.5 mg treatment groups, respectively. Bhavsar et al. [19] reported the incidence of endophthalmitis after IVR injection by means of a standardized procedure that does not require topical antibiotics, sterile gloves, or a sterile drape. Three cases of culture-positive endophthalmitis occurred after IVR injections (0.09%). In all 3 cases of endophthalmitis, topical antibiotics were given for several days after the injection but not before injection. Lima et al. [20] evaluated the safety for bilateral same-day intravitreal injections of anti-VEGF therapy. The incidence of culture-proven endophthalmitis was 0.065%, and the incidence of acute intraocular inflammation was 0.033%. The complication rates after bilateral same-day intravitreal anti-VEG injections seem to be similar to those after unilateral injections. Klein et al. [8] examined 22,579 IVR injections. They identified 10 cases of presumed endophthalmitis (0.044%). Eight of these 10 cases were diagnosed within 4 days of the intravitreal injection. Mean time to diagnosis was 3.5 days. Three of 10 (46%) cases were culture positive. Culture data were not available for 2 of the cases. Only gram positive organisms were isolated: *Staphylococcus epidermidis* × 2, coagulase-negative staphylococcus × 1 (not speciated). Four of the 10 patients returned to baseline vision (±1 line). During the 24 month follow-up of a single-center, prospective study of 138 cases treated with ranibizumab 0.5 mg there were no cases of endophthalmitis [21]. A retrospective analysis of

14,320 IVR injections revealed an incidence of endophthalmitis of 0.02% (1 in 4,500 injections) [22], which is broadly consistent with the rate of 0.05% per injection seen in MARINA study [11] and < 0.1% per injection seen in ANCHOR study [16]. Two recent retrospective reviews of 725 and 981 injections of ranibizumab, respectively, revealed no incidences of endophthalmitis [22,23]. In a multicenter, randomized clinical trial the Diabetic Retinopathy Clinical Network [24] reported 3 injection-related cases of infectious endophthalmitis (1 after a study injection at baseline, 1 after an injection at 4 weeks, and 1 after an injection at 56 weeks) following the 3,973 IVR injections (0.08%) among 375 study participants (0.8%). Ness et al. [25] reported 11 patients with severe intraocular inflammation after intravitreal injection. Only one of them was infectious endophthalmitis with retinal abscess. All others were toxic vitreitis. Seven eyes exhibited hypopyon and five disseminated retinal hemorrhages. The toxic reaction occurred within 48 hours after injection, whereas in the endophthalmitis case, it occurred after 72 hours. They believed that the cause of this reaction was the particular syringe brand used. After changing to another syringe brand, no further cases of toxic vitreitis occurred during the next 6 months. Toxic inflammatory reaction is not only a complication of cataract surgery, but may also occur after intravitreal injection [25]. In the series of Fong et al. [26], the frequency of endophthalmitis was 0.3% (2/648 injections). Recently, Rasmussen et al. [27], in a 4-year longitudinal study of 555 patients treated with ranibizumab for neovascular AMD, found that endophthalmitis occurred in two eyes of 7,584 injections (0.026%). Likewise, in a long-term outcomes of ranibizumab therapy for diabetic macular edema, the RIDE and RISE Research group found that per-injection rates of endophthalmitis remained low over time (0.06% per injection) [28].

In our study, the incidence of culture-positive infectious endophthalmitis following IVR injection was 0.042% (3/7,178 injections). Similar incidences of presumed endophthalmitis (0.03 – 0.077%) have been reported in other recent retrospective studies of intravitreal anti-VEGF agents including ranibizumab [13,29,30]. In the largest consecutive case review series to date (Timothy Murray, communication with AAM), 34,278 patients from the Bascom Palmer Eye Institute and its satellite clinics undergoing treatment with intravitreal anti-VEGF drugs were reviewed between 2005 and 2008, and the per-injection rate of endophthalmitis was found to be 0.039% after IVR injections.

The pathogens most commonly isolated from intravitreal cultures are *Staphylococcus epidermidis* and coagulase-negative staphylococci [8,22,26,29]. Likewise, species of the *Staphylococcus* genus were isolated in our cases no. 1 and 2 (*S. Epidermidis* and *S. Aureus*, respectively). Both cases responded well to treatment and the clinical course was favorable with anatomic and visual improvement. Posteriorly, they received other IVR injections with no complications. *Neisseria* sp. was isolated in our case no. 4, resulting in anatomic resolution but no visual improvement.

The ocular surface bacteria at the time of injection are the likely source of bacteria for postinjection infection [31]. The theoretical likelihood of having high enough concentration of viable bacteria remaining in the volume of tear film potentially displaced into the eye after disinfection by topical application of povidone-iodine to cause endophthalmitis appears to be very low. This seems to be borne

out in our results, in that the incidence of suspected and proven endophthalmitis in our patients was very infrequent.

Difficulty remains in clinically differentiating infectious endophthalmitis from noninfectious endophthalmitis, as there is great overlap between these two entities. In infectious endophthalmitis there is typically an anterior chamber cellular reaction with at least some degree of fibrin, which is associated with pain and scleral or conjunctival inflammation [32,33]. Sterile noninfectious endophthalmitis can present with a hypopyon that may shift with changes in head position, inflammation that is usually only mild and self-limited, and typically there is no pain. As we observed in our case no. 3, the symptoms use to quickly improve with topical or systemic corticosteroids [32,33]. In the present study, the incidence of sterile noninfectious endophthalmitis was only 1 case for total number of 7,178 injections (0.014%). The reported incidence of these cases of noninfectious sterile endophthalmitis for IVR injections is 0.02% to 0.07%, and its etiology is not known [1,16]. Some believe that it is attributable to the preservative, or to endotoxin, but it has been reported after compounded preservative-free triamcinolone [33], and no endotoxin has been found. It is possible that the inflammation may be caused by something in the syringe, needles, or surface of the eye (e.g., povidone-iodine) tracking into the eye with the injection, but not the drug itself [33].

The present study has some obvious shortcomings that should be recognized. It is a retrospective study, nonrandomized, with six participating centers, and without a control group. Its strengths lie on the large number of injections analyzed and the fact that one hundred percent of the injected patients received standardized evaluation and treatment according to the same protocol for intravitreal injections of the Vitreous-Retina Spanish Society (SERV) and with certified technicians to perform the examinations. Moreover, all patients were seen on a follow-up visit four weeks later, so there was no loss to follow-up.

Is there benefit for a theater setting? Although it has been believed that use of a filtered air environment decreases the risk of infection by airborne pathogens, a high percentage of injections take place in the physician's office and the documented low rates of endophthalmitis support the safety of this procedure [12,32]. Additional pros of in-office setting would be cost-effectiveness reasons such as time, expense and facility requirements. Nevertheless, some ophthalmologists are incentivized to perform injections in the operating theater for reasons of reimbursement, and in a single surgeon comparative cohort study in-theatre intravitreal injections were associated with a 13-fold lower risk of endophthalmitis compared to in-office injections [34]. It is difficult to determine whether specific infection precaution measures, particularly the use of drapes, sterile gloves, and prepping of periocular skin have any impact on actual rates of infection [29]. Suggested standardized injection protocols based on expert consensus agree on the use of a lid speculum, preoperative povidone-iodine, appropriate anesthetic, and avoidance of extensive massage to the eyelids [29,32,33]. We draw attention to the use of povidone-iodine, which is considered level 2 evidence in expert opinion. Its use has been associated with a reduced number of colonies and a confirmed lower risk of post-injection infections [35]. In a trial conducted by Speaker et al. [31] where the application of povidone-iodine to the

ocular surface before surgery was compared to the preoperative use of silver solution, a significantly lower incidence of culture-positive endophthalmitis was observed postoperatively in cases where povidone-iodine was utilized prophylactically. This evidence further corroborates the use of povidone-iodine, applied directly to the ocular surface, eyelid margins, and eye lashes before any intravitreal injection [31]. Another important part of the peri-injection protocol is the lid speculum. It is recommended to avoid needle contact with lids and lashes at all times, but its sterility is not mandatory [31]. Furthermore, Fineman et al. [36] has recently described an alternative technique for avoiding contact with the lids and eyelashes without the use of a metal lid speculum along with the results in clinical practice. This technique of bimanual assisted eyelid retraction for intravitreal injection has a low rate of infection similar to the reported rates using a metal lid speculum.

Controversy has revolved around the role of topical antibiotics in the prevention of endophthalmitis, but it is still unclear whether these agents are of any benefit [37]. The rate of endophthalmitis does not seem to be higher when topical antibiotics were not used before, on the day of, or after intravitreal injections [19,38,39]. Despite this debate, it is customary in our services to use post-injection tobramycin prophylactically, due to evidence showing that topical antibiotics lower the number of bacteria cultured from the conjunctiva and lids [40]. Tobramycin is a low-cost, well tolerated antibiotic, which shows a good sensitivity profile against both gram-positive and negative organisms. There is no apparent increase of coagulase-negative staphylococci resistance to tobramycin, as has previously been observed with fluoroquinolones [41].

In conclusion, the rate of culture-proven infectious endophthalmitis associated with IVR injections is low, with an incidence of approximately 1 in 2,392 injections. Patients with this complication do well, typically with a return to baseline vision. We highlight the importance of IVR injections performed with standardized sterile techniques and close follow-up of patients as major contributing factors to such a low occurrence.

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