Incidence and characteristics of acute intraocular inflammation after intravitreal injection of bevacizumab: a retrospective cohort study

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ABSTRACT • RÉSUMÉ

Objective: To determine the incidence and characteristics of acute intraocular inflammation after intravitreal bevacizumab injections from a tertiary care retinal practice.

Design: Retrospective cohort study.

Participants: A consecutive series of patients who had received bevacizumab injections performed by a single surgeon.

Methods: We reviewed the records of all patients with severe anterior chamber inflammation and (or) vitritis after bevacizumab injections.

Results: A total of 693 bevacizumab injections were performed on 193 eyes of 173 patients between June 2006 and March 2008. There were a total of 9 cases of acute intraocular inflammation for an incidence of 1.30% (95% CI: 0.69%–2.47%). All patients had a worse visual acuity at the end of follow-up than on injection day. The mean loss of vision was 6.1 lines of Snellen visual acuity; one patient developed inflammation-induced glaucoma which required surgical intervention.

Conclusions: Intravitreal injection of bevacizumab is associated with a low but significant risk of acute intraocular inflammation and may result in significant visual loss.

Objet : Établissement de l'incidence et des caractéristiques de l'inflammation oculaire aiguë après injections intravitréennes de bévacizumab administrées dans une pratique de soins tertiaires pour la rétine.

Nature : Étude rétrospective de cohorte.

Participants : Examen des dossiers d'une série de patients consécutifs qui ont reçu des injections de bévacizumab administrées par un seul chirurgien.

Méthodes : Nous avons examiné les dossiers de tous les patients qui avaient une sévère inflammation de la chambre intérieure et (ou) un vitritis après des injections de bévacizumab.

Résultats : En tout, 693 injections de bévacizumab ont été administrées dans 193 yeux de 173 patients entre les mois de juin 2006 et mars 2008. On a noté 9 cas d'inflammation oculaire aiguë pour une incidence de 1,30 % (intervalle de confiance de 95 %: 0,69 %–2,47 %). L'acuité visuelle de tous les patients était pire à la fin du suivi qu'au moment des injections. En moyenne, la perte de vision était de 6,1 lignes d'acuité visuelle de Snellen; un patient avait développé un glaucome induit par une inflammation, qui avait requis une intervention chirurgicale.

Conclusions : L'injection intravitréenne de bévacizumab est associée à un risque faible mais significatif d'inflammation intraoculaire aiguë et peut entraîner une perte significative de la vue.

Intravitreal bevacizumab (Avastin, Genentech, San Francisco, Calif.) has been used for several years as an off-label treatment for a variety of ocular diseases, including neovascular age-related macular degeneration (AMD), diabetic macular edema, proliferative diabetic retinopathy, and retinal vein occlusion.[1] Its promising clinical results, low cost, and acceptable side effect profile[2] have made it a popular treatment choice, and thousands of injections are performed in Canada each year.

Acute intraocular inflammation is a well recognized and potentially severe complication of intravitreal bevacizumab. In previous reports its incidence has ranged from 0.14% to 1.49%.[1–5] Patients typically present within the first few days postoperatively with complaints of decreased vision and floaters that often start within 24 hours of the injection.[5,6] Even with aggressive treatment, long-term visual outcome can be poor; in 2 previous reports approximately 50% had visual acuity at long-term follow-up that was worse than on injection day.[5,6] This can be especially devastating for the patients receiving this treatment, since many already have significant visual impairment.

The exact etiology responsible for acute inflammation ("posterior uveitis" or "sterile endophthalmitis") after intravitreal vascular endothelial growth factor inhibitors, and specifically bevacizumab, is not fully understood. It is generally thought to be a severe immunological response to the drug or contaminants. Bevacizumab may present a higher risk than ranibizumab (Lucentis, Genentech, San Francisco,

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Calif.) because of its additional Fc component and corresponding increased protein content.[6] As well, many cases have been linked to a particular "lot" of bevacizumab, suggesting the possibility of contamination.[7] In 2008, 2 separate outbreaks in British Columbia and Saskatchewan were both linked to the same bevacizumab lot.[8–10]

At our centre at Hotel Dieu Hospital in Kingston, Ontario, there were several cases of significant intraocular inflammation noted during the period when predominantly bevacizumab injections were being performed. The purpose of this study was to report our experience with respect to the incidence of acute intraocular inflammation after intravitreal bevacizumab injection and to review the presentation, management, and outcomes of these cases.

Methods

This was a retrospective cohort study based on a chart review of a consecutive series of patients receiving intravitreal bevacizumab injections from a single surgeon (Sanjay Sharma) over a 22-month period (June 2006–March 2008) during which such injections were performed in our centre. Patients were identified by billing information from the surgeon. Data collected from each chart included patient age and sex, date of injection(s), eye, indication(s) for treatment, and visual acuity before the injection. We examined all ophthalmology clinic visits during the week after each injection (normally there are no follow-up visits during this period). Our centre uses centralized electronic and paper medical records, and therefore we could accurately determine whether patients returned to our centre for any reason to the emergency department, emergency eye clinic, or other ophthalmology clinics. We defined acute intraocular inflammation as significant anterior chamber reaction (4–5+ cells or hypopyon) and (or) vitritis. For cases of acute intraocular inflammation we collected additional information, including complaint(s), date, visual acuity at presentation, initial treatment(s), culture results (if applicable), management, and visual acuity at the end of follow-up.

The primary outcome measure was the incidence of acute intraocular inflammation. We calculated 95% confidence intervals (CI) for proportions using the Wilson score method.[11] We also reviewed the presentation, treatment, and follow-up visual acuity of each case. The study was approved by the Research Ethics Board at Queen's University.

Results

Our series consisted of 689 consecutive injections of bevacizumab performed between June 2006 and March 2008. There were a total of 193 eyes of 173 patients (73 males, 100 females, average age at first injection 76.5 [SD 12.1] years). The average number of injections per patient was 3.98 (SD 1.88). Indications for treatment included neovascular AMD (487 injections), diabetes (101 injections), retinal vein occlusion (73 injections), and others (28).

In total there were 9 cases of acute intraocular inflammation following bevacizumab injections for an incidence of 1.30% (95% CI: 0.69–2.47%) of total injections. Table 1 describes the presentation, culture results, and visual outcome of the 9 cases. Eight of the 9 cases occurred after injections during an 11-week period between September 24 and December 10, 2007, and all cases occurred within a 5-month period from July 24 to December 10, 2007. On presentation, 8 of the 9 patients had vitritis and 7 of the 9 patients had a visual acuity worse than on their injection day. Initial treatment of the 9 cases included vitreous tap with injection of antibiotics and steroid (4 cases), prednisolone acetate drops alone (2 cases), and combined prednisolone acetate and fourth generation fluoroquinolone drops (3 cases). One patient received vitreous tap and injection 2 days after unsuccessful medical management. Of the 5 patients having vitreous cultures at some point in the course of their treatment, none grew positive cultures. Intractable inflammatory glaucoma developed in 1 patient, who required surgery to normalize the intraocular pressure. The median length of follow-up was 40 days (range 19–170 days), at the end of which all patients had a worse visual acuity than on injection day. The average loss of vision was 6.1 (SD 6.9) lines of Snellen visual acuity.

Conclusions

Intravitreal bevacizumab is associated with a small but significant risk of intraocular inflammation. In our series of 689 consecutive injections we found the incidence to be 1.30% (95% CI:0.69%–2.47%), which is on the high end of the range of previously reported point estimates. The presentation and management of our cases was somewhat similar to what was described in previous reports. However, in our series, all patients' visual acuity was worse at the end of the follow-up than on injection day, a proportion greater than in previous studies, reporting approximately 50% of patients with visual loss. In addition, our patients lost an average of 6 lines of visual acuity, and some developed profound visual loss despite having only mild to moderate visual loss before injection. Our findings emphasize the potentially serious nature of acute inflammation after intravitreal injection and its potential deleterious effect on vision.

There were several limitations to our study, mainly relating to its retrospective nature. First, given that many patients resided outside our centre's area, it is possible that we may have missed patients with acute intraocular inflammation: if symptomatic, many patients from outside the area likely would have presented to an emergency department or even an ophthalmologist not included in our computerized medical records system and may have never been seen in Kingston if no referral was made. However, even if patients did initially present elsewhere they should have eventually been referred back to the surgeon in Kingston