

Acute anterior uveitis following intravitreal bevacizumab but not subsequent ranibizumab

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Purpose: Previous reports have identified noninfectious uveitis as a potential sequela following both intravitreal bevacizumab and ranibizumab injections. We present two unique cases of acute anterior uveitis following intravitreal bevacizumab that did not occur with subsequent ranibizumab injections.

Methods: Case report.

Conclusion: These cases may reflect differences in the etiology of anterior uveitis following intravitreal bevacizumab and ranibizumab. Given these differences, it may be reasonable to offer ranibizumab to patients who have experienced presumed bevacizumab-induced anterior uveitis.

Keywords: adverse effect, age-related macular degeneration, anterior uveitis, bevacizumab, ranibizumab, uveitis

Introduction

Studies monitoring the safety of intravitreal bevacizumab and ranibizumab injections have identified noninfectious acute anterior uveitis as a sequela of both drugs.^{1,2} Although a large retrospective case series failed to detect a significant difference in the incidence of anterior uveitis after either bevacizumab or ranibizumab,³ randomized prospective trials evaluating this complication are lacking.⁴ We present two cases of acute anterior uveitis following intravitreal bevacizumab that did not recur with subsequent ranibizumab therapy. Uniquely, the first case describes the risk of continued intravitreal bevacizumab following presumed bevacizumab-related acute anterior uveitis, and the second presents a case of unilateral acute anterior uveitis in a patient who had received long-term bilateral intravitreal bevacizumab injections.

Case I

A 75-year-old woman with a history of hypothyroidism received two doses of bevacizumab 8 weeks apart for exudative age-related macular degeneration (AMD) in the right eye. Five days after the second injection, the patient reported tearing, light sensitivity, and decreased vision. The Snellen visual acuity decreased from 20/50 to finger counting. Slit lamp biomicroscopy revealed 1+ conjunctival vascular injection, 1+ corneal edema with intact epithelium, and 1+ flare. Anterior chamber cellular reaction, hypopyon, or vitritis were not documented. A diagnosis of ‘decompensated corneal dystrophy’ was made and sodium chloride hypertonicity ophthalmic ointment 5% (Muro-128[®], Bausch and Lomb, Rochester, NY) and prednisolone acetate 1%

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were initiated. The visual acuity and ocular findings reportedly returned to baseline within 1 week.

On initial presentation at our center 4 months later, the best corrected visual acuity was 20/30. Slit lamp biomicroscopy revealed anterior basement membrane dystrophy but no other corneal pathology or intraocular inflammation. Dilated fundoscopic examination revealed asteroid hyalosis and a serous pigment epithelial detachment without subretinal fluid or hemorrhage. Observation was recommended.

Two months later, the visual acuity dropped to 20/70, and the pigment epithelial detachment increased in height on optical coherence tomography (OCT). The patient underwent a series of 3-monthly intravitreal ranibizumab (0.5 mg/0.05 mL) injections without incident, consistent with reports in the literature supporting the use of anti-vascular endothelial growth factor (VEGF) therapy to treat AMD-associated serous pigment epithelial detachments.^{5,6} The visual acuity subsequently improved to 20/40 with marked resolution of the pigment epithelial detachment on OCT.

Due to patient preference and the diagnostic ambiguity of the original event, maintenance therapy was initiated with a retreatment of bevacizumab. Twelve days later, the patient noted tearing, light sensitivity, and pain in the eye. The visual acuity dropped to 20/100. Slit lamp biomicroscopy revealed 2+ conjunctival vascular injection, corneal edema, and 2+ cell and flare. Dilated funduscopy was stable. The patient was treated with topical prednisolone acetate 1% and homatropine 5% for acute anterior uveitis, and the symptoms resolved completely within 4 weeks. The patient continues to receive monthly ranibizumab injections without relapse of anterior uveitis.

Case 2

A 69-year-old man with a history of diabetes mellitus and primary open-angle glaucoma received a diagnosis of bilateral exudative AMD after reporting a 6-week history of decreased vision. He was initially treated with monthly ranibizumab injections (two in each eye) before switching to bevacizumab. He continued to receive intravitreal bevacizumab injections in each eye every 8 weeks for the next 2 years without complication. Four days after a routine bevacizumab injection in the left eye, he noticed increasing redness and foreign body sensation. The visual acuity dropped from 20/25 to 20/40 and slit lamp examination revealed keratic precipitates with trace cell in the anterior chamber. There was no involvement of the left vitreous cavity or right eye. The eye was treated with topical prednisolone acetate 1% for acute anterior uveitis. After 4 weeks, the anterior chamber

cell and keratic precipitates had resolved. He subsequently received intravitreal ranibizumab injections in each eye every 6 weeks, and tolerated the therapy well with no evidence of recurrent uveitis.

Discussion

The anti-VEGF agents, bevacizumab and ranibizumab, have enhanced the management of exudative AMD.² However, the safety profile of these drugs continues to undergo scrutiny, and noninfectious intraocular inflammation is a known adverse effect of both drugs.¹ A retrospective case series of nearly 2000 injections reported no significant difference between the incidence of post-injection anterior uveitis (1.57% bevacizumab vs 1.38% ranibizumab; $P > 0.80$) or panuveitis (0.39% vs 0.41%; $P = 1.0$).³ However, randomized prospective trials comparing the rates of uveitis between ranibizumab and bevacizumab are lacking, leading some authors to question whether the complication rates are truly similar.^{4,7} Although underpowered to compare this relatively rare outcome, the 1-year clinical trial results from the Comparison of Age-Related Macular Degeneration Treatment Trials reported anterior uveitis in $<1\%$ of study eyes receiving either treatment.⁸

In retrospect, we believe that the first case was bevacizumab-related anterior uveitis that was originally misdiagnosed. AMD treatment later resumed uneventfully with ranibizumab and was then switched to bevacizumab for maintenance therapy. The anterior uveitis promptly relapsed. To our knowledge, this is the first report in the literature to describe recurrent bevacizumab-related anterior uveitis following a retreatment of intravitreal bevacizumab.

The second patient likely experienced bevacizumab-related anterior uveitis after previously tolerating the medication without difficulty, which has been reported.⁹ His case is unique in that he was receiving bilateral bevacizumab injections, yet developed only unilateral anterior uveitis. Both cases corroborate reports from Raja et al¹⁰ and Georgopoulos et al¹⁴ describing the safe administration of intravitreal ranibizumab after bevacizumab-related uveitis.

The etiology of this drug-induced uveitis is speculative at best, since it occurs rarely and there is no histopathologic data with which to correlate the phenomenon. The following mechanisms have been proposed: (1) toxic response to the drug or excipients; (2) direct blood-aqueous or blood-retinal barrier compromise by drug or excipients; (3) immune response to the drug or excipients; and (4) rebound inflammation secondary to VEGF suppression.¹¹

The excipients of both preparations are nearly identical: trehalose dihydrate, sodium phosphate, polysorbate 20, and sterile water (histidine hydrochloride – in ranibizumab only), which makes it more difficult to implicate them in a differential immune response. Moreover, there are no reported cases of hypersensitivity to any of these excipients in the literature.

Alternatively, this reaction may occur as an immunologic response to the Fc protein portion of the full-length antibody molecule itself; ranibizumab is an Fab fragment whereas bevacizumab is a full-length antibody (Fab and Fc) derived from the same parent molecule. This is an attractive explanation since other drugs, such as heparin, provoke a differential immune response based on antigenic load. Unfractionated heparin has a higher propensity to cause heparin-induced-thrombocytopenia than low-molecular weight heparin, presumably due to the larger size of the full heparin molecule and its enhanced ability to form immunogenic complexes with other platelet factors.¹²

The exact immunologic mechanism underlying these cases of uveitis is difficult to ascertain without histopathologic data, though a delayed-type hypersensitivity reaction seems possible given the several-day lapse in time between exposure to bevacizumab and the onset of uveitis symptoms. Interestingly, reports in the cancer literature show that infusions of monoclonal antibodies such as bevacizumab cause immediate hypersensitivity reactions in the majority of cases, though delayed-type reactions can be seen in up to 30% of patients.¹³

Aside from the obvious difference in molecular size between ranibizumab and bevacizumab, it is also possible that differences in drug production could explain the variation in immunogenicity.¹⁴ Bevacizumab is harvested as a glycosylated product of human ovarian cancer cells, whereas ranibizumab is a non-glycosylated product of bacterial metabolism. The glycosylation of bevacizumab creates more potential immunogenic sites compared to the non-glycosylated ranibizumab, which could translate into a higher propensity for bevacizumab to cause inflammatory reactions.

Furthermore, it is interesting to speculate on how the variable dosing regimens for bevacizumab and ranibizumab may contribute to the development of inflammatory complications. The predominant anti-VEGF dosing schedules used for AMD treatment include fixed monthly injections, ‘treat and extend’, and as-needed (pro re nata [PRN]) injections based on symptoms and OCT findings. We could not find anything in the literature to suggest that one dosing regimen may result

in more complications than another, though it would seem reasonable to postulate that more frequent exposure to a drug could result in a higher likelihood of it causing inflammatory/immunogenic complications. Data from the second year of the Comparison of Age-Related Macular Degeneration Treatment Trial may help to more fully elucidate the role that anti-VEGF dosing schedules play in predisposing patients to inflammatory ocular complications.

Despite our conjecture regarding the enhanced immunogenic potential of bevacizumab over ranibizumab, a large retrospective study failed to detect a significant difference in the rates of uveitis between the two drugs.³ Nevertheless, bevacizumab has not been subjected to nearly the same scrutiny (in the form of rigorous clinical trials) as ranibizumab, and thus safety data for bevacizumab is relatively lacking.⁴ The results of future prospective randomized trials comparing the efficacy and side-effect profile of ranibizumab to bevacizumab might help to more definitively answer the questions surrounding the inflammatory sequelae of intravitreal ranibizumab and bevacizumab injections.

Disclosure

The authors declare no conflicts of interest in this work.

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