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 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 1
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%...
were initiated. The visual acuity and ocular findings report-
edly 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 biomicro-
copy revealed anterior basement membrane dystrophy but no
other corneal pathology or intraocular inflammation. Dilated
fundoscopic examination revealed asteroid hyalosis and a
serious 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
retrial 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+ con-
junctival vascular injection, corneal edema, and 2+ cell and
flare. Dilated fundoscopy 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 pri-
mary 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 injec-
tions in each eye every 8 weeks for the next 2 years with-
out 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, random-
ized 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 receiv-
ing either treatment.8

In retrospect, we believe that the first case was bevacizum-
ab-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
retrial of intravitreal bevacizumab.

The second patient likely experienced bevacizumab-
related anterior uveitis after previously tolerating the medi-
cation 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 ranibi-
zumab 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 follow-
ing 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 inflam-
mation 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.

References