



Clinical manifestations of intravitreal bortezomib injection

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ABSTRACT

Purpose: To describe the clinical presentation and ocular manifestations of intravitreal bortezomib.

Observations: Retrospective chart review of five patients who inadvertently received intravitreal injection of bortezomib, instead of bevacizumab, showed that all patients presented hyperacutely within 24–72 hours of the injection with pain and severe vision loss. Examination revealed a fibrinous anterior uveitis, corneal edema, and choroidal effusion associated with a shallow anterior chamber and secondary angle closure glaucoma. Significant vitritis was notably absent. Severe retinal vascular attenuation and optic atrophy, and sometimes even retinal infarction or detachment, followed. Four of the five patients rapidly progressed to no light perception vision. Vitreous gram stain and cultures were negative in all eyes.

Conclusions and importance: Intravitreal bortezomib is severely toxic to the eye. Special safeguards should be instituted for the dispensing of intravitreal medications.

1. Introduction

More than any other treatment in the past decade, intravitreal bevacizumab has revolutionized the management of retinal diseases. Originally developed as a colon cancer therapy, the anti-vascular endothelial growth factor (VEGF) drug bevacizumab quickly found off-label uses for the therapy of retinal disorders, primarily age-related macular degeneration (ARMD) and diabetic retinopathy. Its sibling ranibizumab, developed a few years later by the same company, is FDA-approved for intraocular use in the treatment of exudative ARMD, macular edema due to retinal vein occlusion, and diabetic macular edema. However, bevacizumab use predominates in the community because each dose of ranibizumab costs approximately forty to fifty times more than a dose of bevacizumab.

The CATT (Comparison of Age Related Macular Degeneration Treatment Trial) demonstrated that bevacizumab is non-inferior to ranibizumab for several visual and anatomical outcome measures in ARMD, including average number of letters gained, percent 3-line gainers, and macular thickness.¹ While intravitreal bevacizumab is not FDA-approved for intraocular use, it is used by approximately 60% of retinal specialists treating exudative ARMD.² Infectious endophthalmitis rates are very low for either injection (5 per 10,000)³ but the widespread use of bevacizumab has raised concerns regarding appropriate regulation of compounding pharmacies that prepare bevacizumab for

intravitreal injection.

A cluster of five patients at a Veterans Administration (VA) clinic suffered severe vision loss soon after receiving an intravitreal injection of presumed bevacizumab. Each supplied syringe prepared by the VA pharmacy was labelled “bevacizumab 1.25 mg = 0.05 ml” with the date it was drawn up (that morning). After the first three patients presented to the VA emergency room with similar complaints of vision loss and eye pain, the list of scheduled patients for that injection day was reviewed and patients were proactively called in. It was discovered that a sixth patient was a no-show for treatment, and his syringe was located and quarantined. The syringe was sent to testing laboratories at ASTB Analytical Services, Inc in New Castle, Delaware, whose report revealed that the compound actually in the syringe was bortezomib, and not bevacizumab as labelled. Bortezomib is a chemotherapeutic agent approved for the treatment of multiple myeloma. We describe the clinical presentation of five patients who inadvertently received intravitreal bortezomib.

The views presented in this report are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs. The electronic medical records of the five patients were retrospectively reviewed in detail months after the event, but submission for publication was delayed for years while the cases were in legal review. Data reviewed included Snellen visual acuities, as well as anterior segment and retinal examination findings, before and after injection. Ancillary

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testing results including fundus photography, fluorescein angiography, electrophysiological testing (ERG), and magnetic resonance imaging (MRI) were reviewed for each patient and are described below.

2. Cases

All patients received a single intravitreal injection of presumed bevacizumab at an outpatient clinic on a single day in August 2011 for the treatment of either cystoid macular edema or exudative age-related macular degeneration. Patient age, eye, lens status, indication for treatment, pre-injection visual acuity and final visual acuity are listed in Table 1.

Each patient developed pain and severe vision loss (Counting Fingers to No Light Perception) within 24–72 hours of presumed bevacizumab injection and demonstrated fibrinous anterior uveitis and choroidal effusion associated with corneal edema, a shallow anterior chamber, and elevated intraocular pressure, but no evidence of vitreous cell. All patients received a vitreous tap and intravitreal injection of vancomycin, ceftazidime, and dexamethasone within 3–5 days of presumed bevacizumab injection. All vitreous gram stain and cultures were negative. The retinas failed to demonstrate obvious acute changes, but within weeks, optic atrophy and retinal vascular attenuation were noted. All eyes quickly declined to a visual acuity of no light perception, except for one eye that eventually improved to 20/160 (Table 2). One unused syringe from the compounded batch was quarantined and forwarded for formal forensic analysis. The syringe was found to contain bortezomib.

2.1. Case 1

Patient 1 presented with eye pain one day following intravitreal injection for diabetic macular edema. His visual acuity was reduced from 20/80 to 20/100 with a fixed, dilated pupil and moderate anterior chamber reaction without vitritis or retinitis. He was started on intensive topical steroids, since a sterile inflammatory reaction was suspected given the lack of vitreous cell. Examination the next day revealed a visual acuity of 20/400 and persistent anterior chamber reaction with mild corneal edema. By the third day following injection, the patient developed a small hypopyon with fibrin strands in the anterior chamber and 360° of choroidal effusion without vitritis, retinitis, or optic nerve head edema. Although the suspicion for infectious endophthalmitis was low, the patient underwent a vitreous tap and intravitreal injection of vancomycin, ceftazidime, and dexamethasone. He was started on oral prednisone. By day 5, the patient developed a reverse afferent pupillary defect with resolution of the hypopyon but persistence of corneal edema and fibrin in the anterior chamber. His visual acuity was counting fingers and his pain had resolved completely. The posterior segment exam remained stable. The patient was offered a vitrectomy but declined. By day 11, the anterior chamber reaction was mostly pigmented and the

Table 1
Patient summary.

	Age	Pre-inj VA	Diagnosis	Eye	Lens	Tap & inj Day	Final VA
1	63	20/80	CME, NPDR	OS	PCIOL	3	20/160
2	72	20/60	CME, PDR	OS	NS	3	NLP
3	88	HM	Exudative ARMD	OD	NS	4	NLP
4	52	CF 3ft	CME, sup HRVO, NPDR	OD	NS	5	NLP
5	42	20/30	CME, BRVO	OS	NS	3	NLP

ARMD = age-related macular degeneration, BRVO = branch retinal vein occlusion, CF = count fingers, CME = cystoid macular edema, HM = hand motions, HRVO = hemiretinal vein occlusion, NLP = no light perception, NS = nuclear sclerosis, NPDR = non-proliferative diabetic retinopathy, OD = right eye, OS = left eye, PCIOL = posterior chamber intraocular lens, PDR = proliferative diabetic retinopathy, VA = visual acuity.

Table 2
Clinical manifestations of bortezomib toxicity.

Clinical manifestations of bortezomib toxicity
Fibrinous anterior uveitis
Choroidal detachment
Corneal edema
Secondary angle closure glaucoma
Severe retinal vascular attenuation
Optic atrophy
Retinal infarction and detachment (variable)

choroidal effusion had significantly improved, allowing a better view of the retina that showed severe arterial attenuation in addition to the pre-existing circinate ring of macular hard exudates with scattered intraretinal hemorrhages. There was no retinal infarction or retinal detachment. The patient’s vision improved to 20/160 by week 3 and remained stable thereafter. ERG six months after the initial injection revealed reduced amplitudes for all testing conditions and delayed timing for the 30 Hz flicker cone responses, indicating damage to both the rod and cone photoreceptors (Fig. 1). Rod-mediated responses were reduced by 70% compared to the unaffected eye, while cone-mediated responses were reduced by 45%. Optic atrophy was noted at the one-year exam.

2.2. Case 2

Three days following injection for diabetic macular edema, patient 2 awoke with no light perception vision associated with pain and peri-orbital edema that he reported started 1 day after injection. He was found to have an intraocular pressure of 41 mmHg. Slit lamp examination revealed severe microcystic corneal edema with epithelial sloughing. The anterior chamber was very narrow with inflammatory cells and fibrin but no hypopyon, and the angles were closed. Fundus examination was limited due to the poor view, but 360° peripheral choroidals were visible. Ultrasound revealed a thickened choroid with an engorged ciliary body, but no vitritis or retinal detachment. After treatment with topical glaucoma medications and oral acetazolamide, the pressure normalized to 22. A vitreous tap and intravitreal injection of vancomycin, ceftazidime, and dexamethasone was performed. The patient was also started on topical and oral steroids. The anterior chamber inflammatory reaction improved over the next two weeks along with the patient’s level of pain, but the patient’s vision remained no light perception. Fundus examination at this point revealed peripapillary hemorrhage without significant disc pallor or vitritis, in addition to the pre-existing dense panretinal photocoagulation scars. Follow-up examination three months later revealed a quiet anterior segment with diffuse iris atrophy, as well as optic atrophy and severe retinal vascular attenuation. There was no retinal infarction or retinal detachment. At 6 month follow-up, a brunescant cataract with dense subcapsular cataract precluded detailed fundus viewing. Ten months following the initial injection, electroretinography revealed an extinguished ERG from the affected eye.

2.3. Case 3

Four days following injection for exudative ARMD, patient 3 presented with bare light perception vision and an intraocular pressure of 22 mmHg after treatment at another emergency department with topical glaucoma medications for elevated intraocular pressure. He had mild lid edema and erythema. Slit lamp examination revealed diffuse microcystic corneal edema with moderate anterior chamber inflammation and fibrin, but no hypopyon. There was mild narrowing of the peripheral angles. A hazy fundus examination revealed the pre-existing macular choroidal neovascular membrane with subretinal hemorrhage in the inferior macula, but no vitritis or retinal detachment. Ultrasound revealed a diffusely thickened choroid with a shallow choroidal detachment inferiorly. The patient underwent vitreous tap and

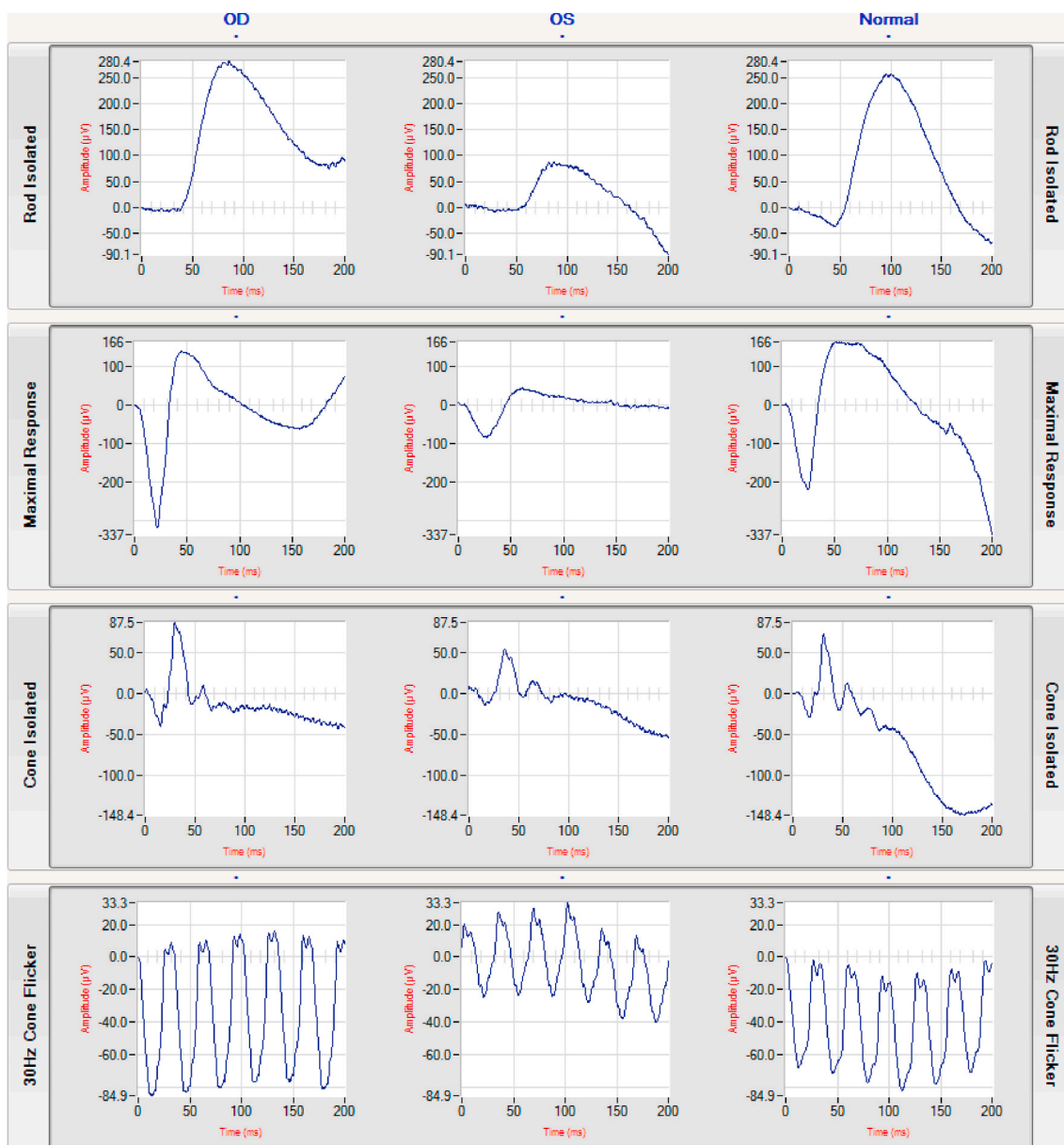


Fig. 1. Electroretinogram of Patient 1 six months after bortezomib injection OS, demonstrating moderate amplitude depression of the scotopic, maximal, and photopic responses in the affected left eye. Responses are entirely normal OD.

intravitreal injection of vancomycin, ceftazidime, and dexamethasone. He was also started on intensive topical steroids. The patient’s visual acuity dropped from LP to no light perception at week 2. The fibrinous anterior uveitis progressed over two weeks before slowly improving. Fundus examination at this point revealed severe vascular attenuation, but again no vitritis or retinitis. There was no optic pallor, retinal infarction, or retinal detachment at last follow-up 3 months after injection.

2.4. Case 4

This patient sought emergency room care for eye pain one day following injection for superior hemiretinal vein occlusion (HRVO)-related macular edema in the setting of nonproliferative diabetic retinopathy. Examination at this time revealed a mild decrease in visual acuity from counting fingers at three feet to counting fingers at one-foot, mild lid swelling, and mild corneal edema, along with a few inflammatory cells in the anterior chamber. Intraocular pressure was 24

mmHg. Fundus examination revealed the pre-existing hemorrhagic superior HRVO associated with macular edema, but no vitritis or retinitis. The following day the anterior chamber shallowed peripherally. Despite intensive topical and systemic glaucoma and steroid therapy, the intraocular pressure rose to 46 mmHg, and the patient developed a severe fibrinous anterior uveitis and progressed to no light perception vision by day 3. Ultrasound revealed a shallow choroidal detachment superiorly but no vitritis (Fig. 2a). Following a vitreous tap and intravitreal injections of vancomycin, ceftazidime, and dexamethasone, the patient’s pain significantly improved although his visual acuity remained no light perception and the intraocular pressure was 30. The fibrinous anterior uveitis persisted over the next three weeks before slowly improving. Approximately one month after the initial injection, an inferior bullous retinal detachment involving the macula was noted. The retinal vessels were sclerotic and the optic nerve head pale. The retinal detachment became complete over the following two weeks and a dense white cataract developed. The patient continued to have severe eye pain and headache over the ensuing months, partially relieved by

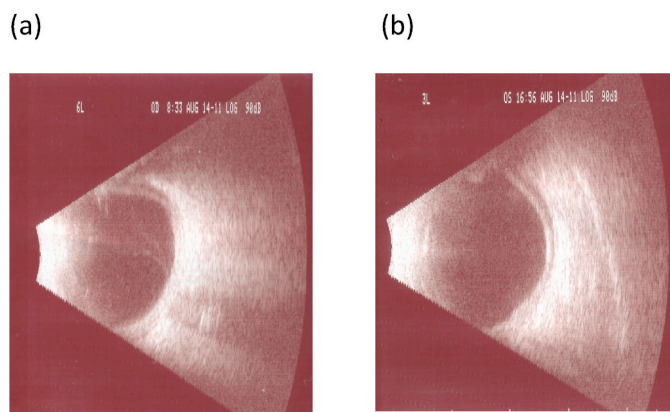


Fig. 2. Ultrasounds of Patient 4 (a) and Patient 5 (b) demonstrating shallow choroidal detachments shortly after bortezomib injection.

botulinum toxin injections.

2.5. Case 5

This patient presented two days following injection for branch retinal vein occlusion-related macular edema with complaints of severe pain for 24 hours and a striking decrease in visual acuity from 20/30 to hand motions. Intraocular pressure was 35 mmHg. Examination revealed mild lid edema and a shallow anterior chamber with prominent flare. Ultrasound revealed a thickened choroid with shallow choroidal detachments without vitritis or retinal detachment (Fig. 2b). Despite intensive topical and systemic glaucoma and steroid therapy, a severe fibrinous anterior uveitis associated with corneal edema developed. Intravitreal injection of vancomycin, ceftazidime, and dexamethasone provided some pain relief but did not prevent progression to no light perception vision by day 5. Fundus examination revealed a cherry red spot with possible optic nerve head hyperemia but no evidence of vitritis. One week following the initial injection, the fibrin had settled into a hypopyon and the patient complained of a recurrence of the orbital pain despite normalization of the intraocular pressure. MRI of the brain and orbits was obtained, which revealed non-specific orbital inflammation. The hypopyon and corneal edema resolved over the next few weeks. Fluorescein angiography revealed the development of superior retinal folds in the area of pre-existing superotemporal retinal hemorrhage, and fundus examination revealed resolution of the cherry red spot with the gradual development of severe arterial attenuation and mild disc pallor compared to prior (Fig. 3). There was no retinal detachment.

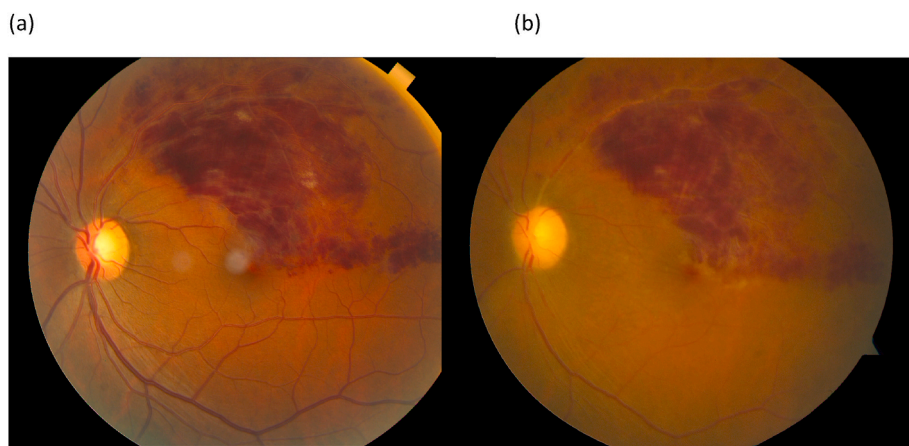


Fig. 3. Fundus photos of Patient 5 who was injected for the treatment of hemorrhagic branch retinal vein occlusion complicated by severe macular edema OS (a) one week before and (b) two weeks after bortezomib injection. Note the optic atrophy, retinal arterial attenuation, and possible retinal pallor that resulted.

Repeat MRI revealed resolution of the orbital inflammatory changes; however, the patient continued to have severe headaches and pain with eye movement, and ptosis developed on the affected side six months after the initial injection. Electrorretinography performed two months later revealed barely detectable dark-adapted responses, whereas light-adapted responses were diminished by approximately 50%.

Since 2011, one of the five patients has died of an unrelated cause. Of the remaining four, three have sought eye care outside of the VA and their ocular status is unknown. Three of the four have post-traumatic stress disorder and depression related to the incident. One patient continues to require long term opiates to control neuropathic pain.

3. Discussion

The clinical presentation of intravitreal bortezomib toxicity can be summarized as a severe fibrinous anterior uveitis associated with corneal edema, a shallow anterior chamber, and angle closure glaucoma caused by choroidal detachment (Table 2). Severe retinal vascular attenuation, optic atrophy, and possibly even retinal infarction or detachment, ensues. All but one of the patients was left with no light perception vision. We don't have a good explanation as to why this one patient was spared total loss of vision. We speculate that reflux of the injected bortezomib or incomplete administration of the intended volume, perhaps due to premature withdrawal of the 30-gauge needle, may have occurred and allowed him to retain some vision.

Bortezomib is an inhibitor of the proteasome, a universal protein complex that is responsible for the degradation of ubiquitinated proteins. One of these proteins is κB , an inhibitor of the transcription factor NF- κB that is essential for inflammatory responses and the growth of immune cells. The plasma cells that replicate uncontrollably in multiple myeloma are particularly sensitive to bortezomib. Bortezomib is relatively non-toxic compared to other chemotherapeutic agents; however, gastrointestinal side effects and thrombocytopenia may develop. Peripheral neuropathy is a dose-limiting side effect that occurs in approximately 30% of patients.⁴ The effects of bortezomib on the retina have not been extensively studied, but this drug may induce apoptosis in retinoblastoma cell lines.⁵ Whereas 1.25 mg of intravitreal bortezomib caused a severe uveitis in our series of patients, systemic bortezomib given at a dose of 0.2 mg/kg to rats suppressed endotoxin-induced uveitis.⁵

The mechanism of neurotoxicity of bortezomib is unclear, but could be proteasome-dependent⁷ or independent⁸ and could represent a direct effect on neurons or a secondary effect from damage to glial cells, possibilities that are not mutually exclusive.

Unfortunately, these five cases do not represent the first time bortezomib has been injected in place of bevacizumab. The similarity in the

names of the two drugs caused a similar compounding error that blinded six people in Portugal in 2009.⁹ When a drug is drawn up and repackaged into syringes for injection at a later time, well thought out protocols must be strictly adhered to with careful reading of all vial and syringe labels, especially if similar sounding names exist for multiple drugs. Careful reading of a vial label with a second person confirming both the generic and brand names on the label before withdrawal and reconciliation with the doctor's order may prevent similar hazardous mix-ups.

Intravitreal injection-related adverse events can never be eliminated, but strict adherence to protocols to maintain sterility and to ensure correct identification of medications is essential. All inflammatory disease post intravitreal injection should be treated presumptively as if it were infectious in nature. However, ophthalmologists should keep in their differential diagnosis list a toxic reaction when patients present with severe vision loss without vitritis soon after an intravitreal injection.

Patient consent

The report does not contain any personal information that could lead to identification of the patients. All patients did give verbal consent to publication of their case.

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Authorship

Both authors attest that they meet the current ICMJE criteria for authorship.

CRedit authorship contribution statement

Chan Nguyen: Conceptualization, Formal analysis, Writing - original draft. **JoAnn A. Giaconi:** Conceptualization, Formal analysis, Funding acquisition, Writing - review & editing.

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