

# A rare case of zoledronate infusion complication leading to glaucoma filtration surgery

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**Abstract:** Zoledronic acid is a nitrogenous biphosphonate commonly used as an intravenous infusion for the management of Paget's disease, osteoporosis, and hypercalcaemia of malignancy. We report a rare and challenging complication of zoledronate infusion: unilateral acute anterior uveitis followed by persistently raised intraocular pressure despite being on four different classes of antiglaucoma medication. The challenge was that the patient required topical steroid to treat her uveitis in the background of known glaucoma with corresponding steroid response. She eventually underwent a left phacotrabeculectomy augmented with 5-fluorouracil. Four weeks postoperatively she developed an encapsulated bleb and underwent needling with 5-fluorouracil. This case highlights the importance of having a high index of suspicion for anterior uveitis in patients with a red and painful eye after initiating biphosphonate therapy. Caution should also be exercised when prescribing biphosphonates to glaucoma patients.

**Keywords:** biphosphonates, anterior uveitis, intraocular pressure

## Introduction

Zoledronic acid is a nitrogenous biphosphonate commonly used as an intravenous infusion for the management of Paget's disease,<sup>1</sup> osteoporosis prophylaxis,<sup>2</sup> and treatment of hypercalcaemia of malignancy.<sup>3</sup> Uveitis is an uncommon ocular complication of zoledronate. The HORIZON (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly)<sup>4</sup> trial in postmenopausal women with osteoporosis showed an absolute increase of only 0.69% in inflammatory ocular adverse events, mainly conjunctivitis, during the first 15 days after infusion in comparison with controls, but no case of uveitis.<sup>4</sup>

Nevertheless, a small number of studies have reported acute anterior uveitis following biphosphonate infusion, including zoledronate.<sup>5-7</sup> The onset of symptoms in most cases is within 72 hours of starting therapy. The majority of cases resolve without sequelae with the administration of topical treatment and cessation of the biphosphonate. However, in our case the acute anterior uveitis was associated with persistently raised intraocular pressure (IOP) despite maximum topical antiglaucomatous treatment, leading to glaucoma filtration surgery and subsequently needling with 5-fluorouracil. To the best of our knowledge this is the first case of this kind to be reported and highlights this rare, and potentially sight threatening, complication of zoledronate infusion.

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## Case presentation

This interventional case report describes a 69-year-old Caucasian lady, on adjuvant letrozole for hormone responsive breast adenocarcinoma, who was also started on the bisphosphonate zoledronate, as prophylaxis against osteoporosis. Within 48 hours of receiving her first zoledronate infusion she developed a red and painful photophobic left eye. She was diagnosed with severe anterior uveitis with corneal edema and plus three cells with a secondary rise in the IOP to 40 mmHg. She had a past history of left episcleritis and had been diagnosed with primary open angle glaucoma 11 years earlier with advanced cupping bilaterally. She had already had glaucoma surgery in her right eye and was known to be a steroid responder.

During follow-up, IOP remained high in the left eye over a 4-month period, fluctuating between 26 mmHg and 42 mmHg, despite being on four antiglaucoma medications (latanoprost, Cosopt<sup>®</sup>, acetazolamide 250 mg twice daily). The challenge was that she required topical steroid (Pred Forte<sup>®</sup>) drops to treat her uveitis in the background of known glaucoma and steroid response. A previous episode of postoperative uveitis in the fellow eye demonstrated she could not be controlled effectively with weaker steroid (rimexolone). In this context, stronger steroids were used to control the inflammation. The persistently raised IOP resulted in early visual field loss and she underwent a left phacotrabeculectomy with 5-fluorouracil (25 mg/mL). This lady's severe uveitis was maximally controlled by Pred Forte. Given that her presenting pressure was 40 mmHg, her raised IOP was in part due to inflammation. Therefore, treating the uveitis was the immediate concern. The balance was controlling the inflammation so that we could speedily carry out glaucoma surgery, versus tolerating a spell of high pressure (largely controlled by antiglaucoma medication).

With a previous history of uveitis, not surprisingly, 4 weeks postoperative she developed an encapsulated bleb with an IOP of 51 mmHg and underwent needling with 5-fluorouracil. Four weeks post-needling, an injected diffuse bleb was noted with persistently raised IOP (26–33 mmHg), with an element of steroid response. Her visual acuity remained stable at 6/6. Eventually IOP was controlled at 17 mmHg with no topical medication, careful postoperative follow-up, bleb massage, and cessation for the need for topical steroids.

## Discussion

The use of bisphosphonates is indicated in osteoporosis, bony metastases with hypercalcemia, and Paget's disease

due to their ability to inhibit osteoclastic activity and bone resorption. Bisphosphonates have great affinity for calcium and therefore preferentially accumulate in the bone. Common side effects from bisphosphonates include dysphasia, influenza-like symptoms, myalgia, and arthralgia. Ocular complications include nonspecific conjunctivitis, episcleritis, scleritis, uveitis, and optic neuritis.<sup>8–10</sup> Interestingly, acute anterior uveitis is more common in bisphosphonates containing nitrogen (alendronate, pamidronate, zoledronate, risedronate), although in one report uveitis has been associated with bisphosphonates not containing nitrogen (clodronate, etidronate).<sup>11</sup> The inflammatory mechanism remains unclear, but may be related in part to higher levels of proinflammatory cytokines (interleukin-6 and tumor necrosis factor-alpha) caused by bisphosphonates.<sup>12</sup>

On resolution of the initial uveitic episode, various management options have been attempted. Some patients have been switched to a different drug of the same class, with some observing decreased inflammation and some not noticing any relapse at all, suggesting immunological tolerance.<sup>13</sup> Recurrence of ocular inflammation has also been shown to occur on rechallenge with the same drug,<sup>14</sup> and it has been suggested that the offending drug should be discontinued in order to prevent involvement of the contralateral eye and recurrent or chronic ocular inflammation. Patients who are susceptible to nitrogen-containing bisphosphonates should be switched to the non-nitrogen-containing bisphosphonates. The safety of repeating the infusions of zoledronic acid in these patients, even with prophylactic topical steroids and atropine, has not been established.

## Conclusion

In summary, the indications for bisphosphonates are clear and their benefits proven. Our case serves to illustrate a rare complication of anterior uveitis following treatment in a patient with a known history of glaucoma and eye surgery. The management was challenging, but successful. Had the acute anterior uveitis presented in the right eye with a previous trabeculectomy, the management would have been more complicated and sight threatening. This rare case emphasizes the importance of exercising caution when prescribing bisphosphonates to glaucoma patients. A high index of suspicion is needed in patients with a red and painful eye for anterior uveitis after initiating bisphosphonate therapy.

## Disclosure

The authors report no conflicts of interest in this work.

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