# Zoledronate-Associated Orbital Inflammation: A Case Series and Literature Review

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## ABSTRACT

**Introduction:** Bisphosphonates are known to cause acute systemic inflammation through stimulation of proinflammatory cytokines. This reaction can include conjunctivitis, anterior uveitis, episcleritis, scleritis, and, rarely, orbital inflammation. We present 2 cases of zoledronate-associated orbital inflammation and a literature review highlighting treatment challenges.

**Case Presentation:** The first case was managed with intravenous (IV) methylprednisolone, 1 mg/kg, followed by a short steroid taper. Symptoms recurred after completion of the taper. The second case presented with optic perineuritis and preseptal and postseptal inflammation. Initial treatment with IV methylprednisolone, 1 mg/kg, resulted in incomplete response, necessitating escalation to high-dose corticosteroid therapy.

**Discussion:** A literature review identified 19 additional cases of zoledronate-associated orbital inflammation. There was no clear consensus regarding treatment and only 1 reported case of relapse was identified.

**Conclusions:** We recommend initial treatment with IV methylprednisolone, 1 mg/kg, followed by a prolonged taper. If symptoms do not improve within the first day of treatment or if the optic nerve sheath is involved, escalation to IV methylprednisolone, 1 g daily, may be warranted.

## INTRODUCTION

Bisphosphonates are a class of pharmaceuticals commonly prescribed for osteoporosis, Paget disease, osteoclastic bone metastases, and multiple myeloma. These medications bind to the bone hydroxyapatite matrix and inhibit osteoclast function, thus preventing bone resorption and relieving bone-related pain.[1] One well-known adverse effect of bisphosphonates is a systemic inflammatory state called the acute-phase response, characterized by fever, fatigue, and nausea within 72 hours of administration and thought to result from transient stimulation of proinflammatory cytokines.[2] In addition to systemic inflammation, bisphosphonates are known to cause ocular inflammation, most commonly conjunctivitis, anterior uveitis, episcleritis, and scleritis.[3]

In rare cases, orbital inflammation has also been associated with bisphosphonates.[4-22] Bisphosphonate-associated orbital inflammation can present with a variety of symptoms that mimic infection, including fever, nausea, ocular pain, diplopia, restricted eye movements, conjunctival injection, chemosis, and periorbital edema.[23] Given the rare association between bisphosphates and orbital inflammation, diagnosis is often delayed, and there is no clear consensus on treatment.

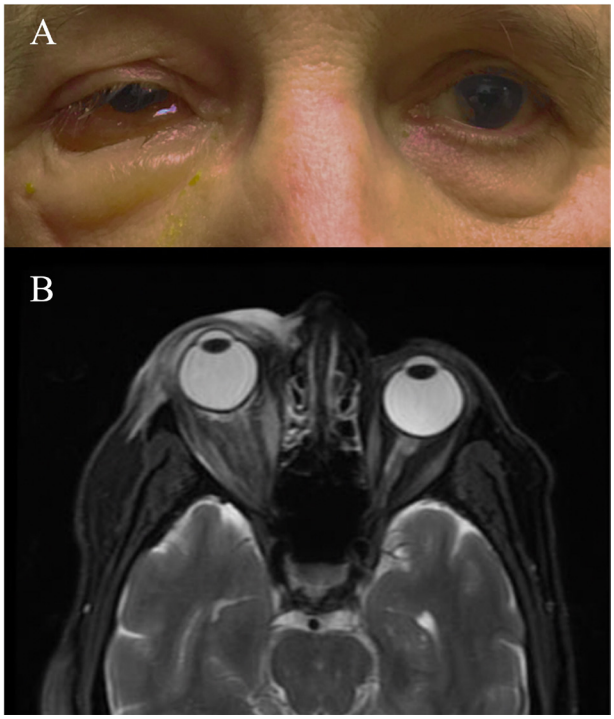
We present 2 cases of orbital inflammation following zoledronate infusion, along with a literature review of the manifestations and management of zoledronate-associated orbital inflammation. All data handling was compliant with the Health Insurance Portability and Accountability Act and the Declaration of Helsinki. The first case was notable for recurrent inflammation following a steroid taper, which has only been described once previously. The second case was notable for optic perineuritis and required higher doses of intravenous (IV) steroids to achieve remission. Management of both cases was challenging because of the limited guidance available in the literature. Thus, the aim of this review is to describe the reported cases of zoledronate-associated orbital inflammation and offer guidance on treatment.

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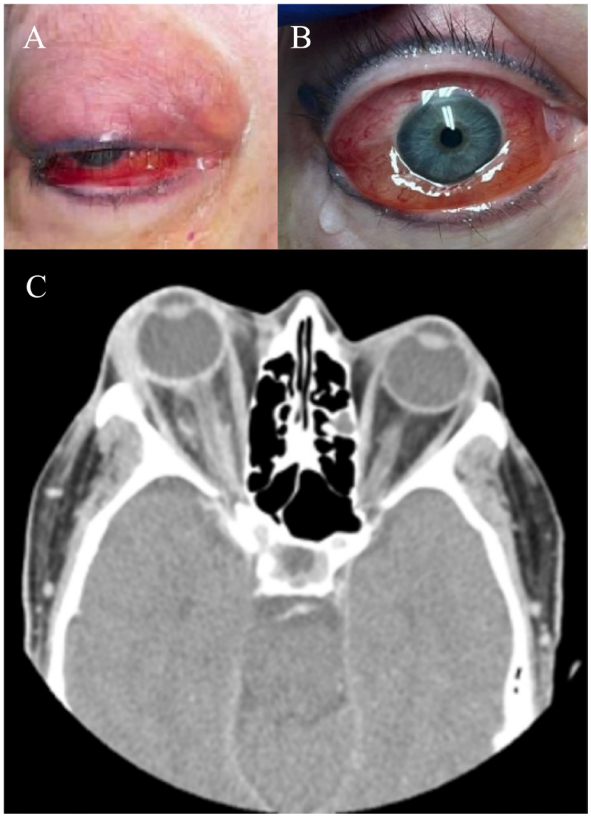
**Figure 1.** Case 1 Presentation




A) Initial presentation of a 72-year-old man presenting with right eye pain, proptosis, and chemosis three days after zoledronate infusion (Case 1).

B) T2-weighted magnetic resonance imaging orbit from the initial presentation of Case 1 demonstrating right-sided diffuse preseptal and postseptal edema and fat stranding with extraocular muscle thickening.

**Figure 2.** Case 2 Presentation




A-B) Initial presentation of a 60-year-old woman presenting with weakness, fever, chills, vomiting, right eye pain and swelling, and photophobia.

C) Contrast-enhanced computed tomography orbit from the initial presentation of Case 2 demonstrating right-sided diffuse pre- and post-septal edema and fat stranding with optic nerve sheath enhancement.

## CASE PRESENTATION

### Case 1

A 72-year-old man presented with headaches, vomiting, and right eye pain and swelling 3 days after his first zoledronate infusion for prostate cancer bone metastases. His medical history was notable for hypertension, hyperlipidemia, and coronary artery disease. Best-corrected visual acuity was 20/20 in the right eye and 20/20 in the left eye. Intraocular pressure, pupils, and confrontational fields were within normal limits bilaterally. There was no relative afferent pupillary defect. Right eye abduction and depression were mildly limited. There was 6 mm of relative proptosis and chemosis (Figure 1A). Dilated fundus examination revealed no optic disc edema. Magnetic resonance imaging (MRI) revealed diffuse preseptal and postseptal edema and fat stranding with extraocular muscle thickening (Figure 1B). Pain, proptosis, and chemosis improved rapidly with 1 dose of IV methylprednisolone, 1mg/kg; however, inflammation recurred after a 9-day taper of oral prednisone (80 mg for 5 days, 60 mg for 1 day, 40 mg for 1 day, 20 mg for 1 day, and 10 mg for1 day), necessitating a longer prednisone taper (40 mg for 1 week, 30 mg for 1 week, and 20 mg for 1 week before resumption of the patient's maintenance dose of prednisone, 10 mg daily, for prostate cancer).

### Case 2

A 60-year-old woman presented with weakness, fever, chills, vomiting, photophobia, and right eye pain and swelling 20 hours after a zoledronate infusion for osteoporosis. Her medical history was notable for hypertension, hyperlipidemia, hypothyroidism, and type 2 diabetes. Best corrected visual acuity was 20/30 in the right eye and 20/20 in the left eye. Color vision, pupils, and confrontational fields were within normal limits bilaterally. There was no relative afferent pupillary defect. Right intraocular pressure was 24 mm Hg, compared with 22 mm Hg in the left eye. Motility of the right eye was moderately limited in all directions except supraduction. Examination revealed right upper eyelid erythema and conjunctival chemosis (Figure 2A-B). Dilated fundus exam revealed no optic disc edema. Imaging demonstrated preseptal and postseptal edema and fat stranding with optic nerve sheath enhancement (Figure 2C). IV antibiotics were administered because of concern for infection; however, there was no improvement over 24 hours. Treatment with IV methylprednisolone, 1 mg/kg, was initiated with immediate improvement in pain, chemosis,

**Table.** Literature Review of Zoledronate-associated Orbital Inflammation, Plus Current Cases

| Publication | Age (Sex) | Time From Last Dose to Onset | Indication for Zolendronate | Other Medical History | Sites of Orbital Inflammation | Treatment[a] | Time to Resolution |
|---|---|---|---|---|---|---|---|
| Sharma, et al; 2008[4] | 57 (M) | 3 days | Knee osteonecrosis | None listed | Preseptal, postseptal | 1g IV MP for 3 days, then oral pred taper | 3 days |
| Phillips, et al; 2008[5] | 55 (M) | 1 day | Metastatic renal cancer | None listed | Preseptal, postseptal | 60 mg oral pred tapered for 10 weeks | 3 days |
| Seth, et al; 2009[6] | 68 (M) | 1 day | Metastatic prostate cancer | HTN | Preseptal, postseptal, scleritis, AION | 100 mg oral pred | 7 days |
| Missotten, et al; 2010[7] | 71 (M) | Minutes | Metastatic prostate cancer | None listed | Preseptal, postseptal for 3 weeks | 32 mg oral pred | 5 days[b] |
| Yeo, et al; 2010[8] | 62 (M) | 1 day | Charcot arthropathy | Type 1 diabetes | Preseptal | None listed | 10 days |
| Yang, et al; 2010[9] | 89 (F) | 3 days | Osteoporosis | None listed | Preseptal, postseptal, scleritis, optic perineuritis, myositis | 1g IV MP for 3 days, then oral pred taper | 3 days |
| Procianoy, et al; 2010[10] | 60 (F) | 1 day | Osteoporosis | Autoimmune thyroiditis, breast cancer | Preseptal, postseptal | 80 mg oral pred tapered for 6 weeks | 12 days |
| Ortiz-Pere, et al; 2011[11] | 70 (F) | 1 day | Paget disease | None listed | Preseptal, postseptal | Oral pred for 3 weeks | 21 days |
| Kaur, et al; 2011[12] | 57 (F) | Several hours | Osteoporosis | Esophageal, breast, lung cancer | Preseptal, postseptal | 2 MP dose packs | 14 days |
| Schwab, et al; 2012[13] | 55 (F) | 4 days | Osteoporosis | Type 1 diabetes, hypothyroidism, osteoarthritis, GERD | Preseptal, postseptal, scleritis, optic perineuritis, myositis | 1g IV MP for 2 days, then 60 mg oral pred tapered for 3 weeks | 7 days |
| Boni, et al; 2013[14] | 75 (F) | 2 days | Osteoporosis | None listed | Preseptal, postseptal, anterior uveitis | IV MP | Several days |
| Rahimy, et al; 2013[15] | 68 (M) | 1 day | Osteoporosis | None listed | Preseptal, postseptal | 1g IV MP for 3 days then 60 mg oral pred tapered for 5 weeks | 3 days |
| Manuylova, et al; 2015[16] | 66 (M) | 4 days | Osteoporosis | HTN, HLD, GERD | Preseptal, postseptal, optic perineuritis, anterior uveitis | High-dose oral pred | After treatment |
| Umanakwe, et al; 2017[17] | 68 (F) | 12 hours | Osteoporosis | HTN, HLD, depression/ anxiety, migraines | Preseptal, postseptal, scleritis, anterior uveitis | 1g IV MP for 1 day, then then 60 mg oral pred tapered for 10 weeks | 80 days |
| Herrera, et al; 2019[18] | 56 (F) | 1 day | Osteoporosis | Sjogren's syndrome, SLE, inflammatory demyelinating polyneuropathy | Preseptal, postseptal, scleritis, optic perineuritis | 50 mg oral pred for 1 week, then slow weekly taper | 7 days |
| Chehade, et al; 2019[19] | 65 (F) | 4 days | Osteoporosis | Lymphoma, breast cancer anterior uveitis | Preseptal, postseptal, scleritis, optic perineuritis, weeks | Topical prednisolone 3x/day tapered for 5 | 35 days |
| Keren, et al; 2019[20] | 58 (F) | Several hours | Metastatic thyroid cancer | None listed | Preseptal, postseptal, scleritis, anterior uveitis | None listed | 14 days |
| Khalid, et al; 2021[21] | 62 (M) | 3 days | Metastatic prostate cancer | Type 2 diabetes, HLD, AAA | Preseptal, postseptal | 1mg/kg oral pred | 7 days |
| Faryal, et al; 2021[22] | 45 (M) | 3 days | IgG kappa myeloma | None listed | Preseptal, postseptal | 500 mg IV MP for 3 days, then 60 mg oral pred taper | 21 days |
| Arzbecker, 2025[d] | 72 (M) | 3 days | Metastatic prostate ancer | None listed | Preseptal, postseptal | 1mg/kg IVMP for 1 day, then 80 mg oral pred taper for 9 days | 30 days[c] |
| Arzbecker 2025[d] | 60 (F) | 20 hours | Osteoporosis | HTN, HLD, GERD, type 2 diabetes, hypothyroidism | Preseptal, postseptal, optic perineuritis | 1mg/kg IV MP for 1 day, then 1g IV MP for 3 days, then 80 mg oral pred tapered for 8 weeks | 21 days |

Abbreviations: AAA, abdominal aortic aneurysm; AION, anterior ischemic optic neuropathy; CAD, carotid artery disease; F, female; GERD, gastroesophageal reflux disease; HLD, hyperlipidemia; HTN, hypertension; IgG, immunoglobulin gamma; IV MP, intravenous methylprednisolone; M, male; pred, prednisone; SLE, system lupus erythematosus.

[a]Where the type of medication but not the dose was published, the same information is included in the treatment column.

[b]Recurred 7 months later.

[b]Recurred and required 4-week taper.

[d]Case presented in this report.

and extraocular movements, but symptoms recurred completely within 24 hours. Given the limited initial response to treatment and imaging findings of optic perineuritis, the steroid dosage was increased to IV methylprednisolone, 1 g daily, for 3 days, which is standard treatment for optic neuritis.[24] The patient was then transitioned to oral prednisone, 80 mg daily (slightly less than 1 mg/kg), which was successfully tapered over 8 weeks.

## LITERATURE REVIEW

A PubMed literature search was conducted using combinations of medication-related terms (zoledronate, zoledronic acid, Aclasta, Zometa, Reclast) and orbital terms (orbit, orbital, orbitopathy). Abstracts without full-text articles were excluded. This search identified 28 cases of zoledronate-associated orbitopathy, of which 19 had full-text reports available for review (Table).[4-22] The median age of patients was 62 years, and 53% were female. Zoledronate was indicated for osteoporosis (53%), cancer with bone metastasis (26%), osteonecrosis (5%), Paget disease (5%), Charcot arthropathy (5%), and IgG kappa myeloma (5%). All cases presented with unilateral ocular pain and swelling and occurred within 4 days of the most recent infusion. The median onset of symptoms was 1 day after infusion. All cases treated with steroids reported improvement in symptoms on the first day of treatment, and the median time to complete symptom resolution was 7 days. Patterns of inflammation included preseptal and postseptal inflammation (95%), scleritis (37%), optic perineuritis (26%), myositis (11%), anterior uveitis (26%), anterior ischemic neuropathy (5%), and preseptal inflammation (5%). Patients typically received IV steroids (37%) or oral steroids (47%), with 1 patient receiving topical steroids (5%) and 2 patients receiving no reported treatment (11%). Starting doses varied widely. Among those receiving systemic steroids, doses ranged from oral prednisone, 32 mg, to IV methylprednisolone, 1 g (equivalent to approximately 800mg oral prednisone).

## DISCUSSION

Orbital inflammation is a rare adverse reaction to bisphosphonates. Specifically, IV aminobisphosphonates (zoledronate, ibandronate, alendronate) have been reported to induce orbital inflammation. This is thought to be due to the presence of a nitrogen group involved in sensitization and activation of macrophages and osteoclasts, which are derived from macrophages. Activation of these cell types stimulates the release of proinflammatory cytokines, causing an acute-phase response. Up to 40% of patients receiving IV aminobisphosphonates experience an acute-phase response within 3 days of administration.[2] All reported cases of zoledronate-associated orbital inflammation occurred within a similar time frame (within 4 days) and mimicked infection, with prodromal symptoms of unilateral orbital pain and swelling. Therefore, it is hypothesized that the proinflammatory cytokines involved in the acute-phase response are responsible for inducing orbital inflammation.

Currently, steroids are the standard treatment for bisphosphonate-associated orbital inflammation; however, no consensus exists regarding appropriate dosing. Among reported cases of zoledronate-associated orbital inflammation, approximately half of patients received IV steroids and half received oral steroids. Many authors described dosing at 1mg/kg, which is typical for idiopathic orbital inflammation. Despite differences in dose and duration, all cases reported improvement in symptoms on the first day of treatment and complete resolution thereafter. Only 1 case experienced a relapse 7 months later.[7]

Here, we present a second case of recurrent inflammation occurring 10 days after treatment with IV methylprednisolone, 1 mg/kg. This was likely due to the rapid steroid taper, given that the patient remained in remission after a longer taper. Additionally, we describe the first reported case of incomplete initial treatment with IV methylprednisolone, 1 mg/kg. For this patient, treatment was escalated to IV methylprednisolone, 1 g daily, for 3 days, resulting in immediate improvement in symptoms and sustained remission after an 8-week oral prednisone taper. This case was notable for optic nerve sheath involvement. Two previously reported cases with optic perineuritis were treated with IV methylprednisolone, 1 g daily, for 2 to 3 days. Symptoms improved rapidly and did not recur.[9,13] Thus, the presence of optic perineuritis may necessitate a higher initial steroid dose.

## CONCLUSIONS

Bisphosphonate-associated orbital inflammation should be suspected in any patient presenting with acute orbital inflammation within several days of an aminobisphosphonate infusion. We recommend treating newly diagnosed bisphosphonate-associated orbital inflammation with IV methylprednisolone, 1 mg/kg/day (or the oral equivalent), for 1 week, followed by a slow taper over 3 to 4 weeks. If symptoms do not improve on the first day of treatment, or if there is optic nerve sheath involvement, escalation to IV methylprednisolone, 1 g daily, should be considered.

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