**Supplementary Table 1.** Case reports of zoledronate associated ocular inflammation.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Cases** | **Gender** | **Age****(years)** | **Indication for bisphosphonate** | **Onset of symptoms** | **Symptoms** | **Signs** | **Imaging** | **Vision of affected eye** | **Treatment** | **Time to resolution** |
| Missotten *et al* (2010) (19)  | M | 71 | Metastatic prostate cancer | N/A | Unilateral* Pain
 | * Mild lid swelling
* Conjunctival injection and chemosis
* Subconjunctival hemorrhage
* proptosis
 | CT* Proptosis
* Fat stranding

Ultrasound* No scleritis
 | 20/25 | Oral prednisone  | Complete resolution in 5 days  |
| Yeo *et al* (2010) (20)  | M | 62 | Charcot arthropathy | Within 24 hours | Bilateral* Nausea
* Blurry vision
* Pain
 | * Periorbital edema
* Conjunctival injection
* Chemosis
* Proptosis
 | CT* No evidence of orbital cellulitis

MRI* Supraorbital soft tissue swelling
 | 20/20 ODHM OS (baseline poor vision OS eye) | None | Graudal recovery over 10 days |
| Kaur *et al* (2011) (21)  | F | 57 | Osteoporosis | Within several hours | Unilateral* Pain
* Photophobia
 | * Lid edema
* Conjunctival injection
* Elevated IOP
 | CT* Preseptal and retroseptal inflammation
* Thickened sclera
 | Unchanged visual acuity from baseline | Oral prednisone followed by oral methylprednisolone | Complete resolution in 2 weeks |
| Ortiz-Perez *et al* (2011) (22)  | F | 70 | Paget’s disease | With in 24 hours | Unilateral* Pain
 | * Proptosis
* Conjunctival injection and chemosis
* Lid swelling
* ophthalmoplegia
 | CT* Diffuse orbital inflammation
 | N/A | Oral prednisone  | Significant improvement in 1 daysComplete resolution in 3 weeks  |
| Peterson *et al* (2012) (12) | F | 56 | Osteoporosis | 12 hours | Unilateral* Pain
* Headache
* Blurry vision
 | * Lid edema
* Conjunctival injection
* Chemosis
* Proptosis
* Decreased extraocular muscle movement
* Anterior chamber cells
 | CT* Intraconal and extraconal fat stranding
 | 20/40 | One dose of IV methylprednisoloneOral Prednisone | Almost completely resolution in 2 days |
| Belliveau *et al* (2012) (23)  | F | 58 | Osteoporosis | 10 hours | Bilateral (left worse then right)* Ocular irritation
* Redness
* Photophobia
* Headaches
* Generalized weakness, pain and nausea

1 day after symptom onset * Rash on all four limbs and on trunk
 | * Anterior chamber cells and flare in left eye.
 | None | 6/6 | Topical prednisolone acetate, dexamethasone ointment and homatropine. | Uveitis resolved within 4 weeksAt initial presentation the C-reactive protein was 30mg/L but normalized to 1.8 mg/L |
| Böni *et al* (2013) (24)  | F | 75 | Osteoporosis | 2 days post infusion | Bilateral (left worse then right)* Pain
* Swelling
 | * Ophthalmoplegia
* Conjunctival chemosis and hyperemia
* Proptosis of left eye
* Mild bilateral anterior uveitis
* Choroidal folds in left eye
 | CT* Intraconal and extraconal fat staining.
* Left sided proptosis

MRI* Diffuse lid, orbital fat and scleral enhancement
 | OD 0.8 ratio OS 0.2 ratio | Topical steroids and cycloplegia 1g IV methylprednisolone for 3 days followed by oral prednisone taper | Complete resolution of inflammation within days but visual acuity returned to 0.9 one week after starting treatment |
| Rahimy *et al* (2013) (13) | M | 68 | Osteoporosis | 1 day | Unilateral * Periocular pain
* Swelling
* Blurry vision
* Pain with extraocular movement
* Chills, fatigue and malaise
 | * Upper lid edema
* Conjunctival chemosis and hyperemia
* Anterior chamber inflammation
* Restricted extraocular movements in all gaze
 | CT* Preseptal and postseptal fat stranding
* proptosis
 | 20/50 | 1 g IV methylprednisolone for 3 days followed by oral prednisone taper | Ocular/orbital Inflammation nearly resolved and the vision returned to baseline (20/25) after 3 days |
| Freitas-Neto *et al* (2013) (25)  | F | 66 | Osteoporosis | 2 days | Unilateral * decree vision
 | * Anterior chamber cells and flare
* Opacification the anterior vitreous
* Vitreous haze
 | Ocular ultrasound* Showed absence of vitreous opacity
* No other retinal pathology
 | 20/60 | Topical steroids and cycloplegia drops | 48 hours after the ocular symptoms resolved, vision was normal, and trace cells present in anterior chamber Normal dilated fundus exam (no vitreous cells)Complete resolution of inflammation in 1 week |
| Vora *et al*(2014) (26)  | 2 F | 63, 77 | Osteoporosis | Within 5 and 7 days | Unilateral* Pain
* Swelling
* Redness
* Diplopia (in 1 case)
 | * Periorbital edema
* Conjunctival injection and chemosis
* Proptosis
* Restricted extraocular movements
 | MRI* Subtle thickening of sclera and slight enlargement of lateral rectus

CT* Periorbital soft tissue swelling
* Scleritis
* Orbital fat stranding
* Proptosis
* Enlarge lacrimal gland
 | Range 20/20 to 20/30 | IV dexamethasone followed by oral prednisone taper | Symptoms improved within 24-48 hours Complete resolution ranged within 2 to 3 months |
| Cavallasca *et al* (2014) (27)  | F | 59 | Osteoporosis | 2 days | Unilateral* Pain
* redness
 | * conjunctival hyperemia
* Anterior chamber cells and flare
* Normal fundus exam
 | None | Preserved | Topical prednisolone and atropine | 2 weeks |
| Muruganandam *et al*(2016) (28)  | F | 65 | Osteoporosis | 2 days | Unilateral * Pain
* Watery discharge
* Diplopia
 | * Myosis
* Conjunctival chemosis
* Proptosis
 | MRI* Enhancement in the intra-orbital retro-orbital fat involving the optic nerve sheath.
 | N/A | Oral prednisone | Complete resolution in 1 week |
| Tian *et al* (2016) (29)  | F | 63 | Osteoporosis2 year history of tolerance to oral alendronate | 1 day | Bilateral* Irritation
* Swelling
* Blurry vision
* diplopia
 | * Uveitis
* Macular edema
 | None | N/A | Topical steroidOral steroids (did not report name) | Complete resolution (did not report time) |
| Lefebvre *et al* (2016) (30)  | 3 F2 M | 46-79 | Osteoporosis Metastatic lung adenocarcinoma | Average 4.6 days (range 1-11 days) | Unilateral* Pain
* Pain with ductions
* 1 had viral-like prodrome
 | * periorbita erythema and edema
* Chemosis
* limitation of extraocular muscle movements
* Proptosis
 | CT and MRI* Diffuse retrobulbar orbital inflammation
* Myositis
 | N/A | One patient did not receive any anti-inflammatory treatment One patient had 1 dose of IV methylprednisone3 patient on oral prednisoneOne patient on oral dexamethasone  | Resolution range of 1 day to 4 weeksPatient without anti-inflammatory treatment had spontaneous resolution in 2 weeks |
| Umunakwe *et al* (2017) (11) | F | 68 | Osteoporosis | Within 12 hours | Unilateral* Pain
* Photophobia
* Blurry vision
* Fever
* Myalgias

Arthralgias | * Conjunctival injection
* Anterior chamber cells
* Hypopyon
* Hyphemia
* Scleritis
* Proptosis
 | CT* Scleral thickening
* Proptosis
* Fat stranding

B-scan* Thickened sclera
* T-sign
 | 20/50 at presentation20/400 at day 2 follow-up | One dose of 1g IV methylprednisoneOral PrednisoneTopical steroids and cycloplegic | Significant improvement in 2 days and complete improvement in 10 weeks. Final VA 20/20 |
| Haider *et al*(2017) (31)  | M | 60s | Paget disease | Within 24-48hrs | Bilateral* Photophobia
* Redness
* Tearing
* Blurry vision
* Myalgias and malaise
 | * Subconjunctival hemorrhages
* Anterior segment cells and flare
* Normal fundus
* exam
 | None | 6/5 | Topical dexamethasone, homatropine | Complete resolution within 2 weeks |
| Jun *et al*(2017) (32)  | F | 47 | Breast cancer with bone metastasis | 4 days | Bilateral* Pain
* Redenss
* Chills and myalgia
 | * Conjunctival injection
* Anterior chamber cells
* Normal fundus exam
 | OCT normal | 20/20  | Topical steroids, bromfenac, and cycloplegic drops | Resolution after 1 week |
| Kennedy *et al* (2018) (33)  | 2 F | 78, 80 | Breast cancer, Paget’s disease | 1 day | Unilateral* Pain
* Redness
* Photophobia
* Decreased vision
 | * Conjunctival hyperemia and chemosis
* Subconjunctival hemorrhage
* Anterior chamber cells (all cases), flare, and fibrin
* One case has 1mm hypopyon
 | None | Range 6/36 to CF | Topical steroids and cycloplegia  | Resolution of inflammation was seen over 1 to 3 weeks  |
| Keren *et al*(2019) (2) | 2 F | 58, 63 | Osteoporosis, Metastatic thyroid carcinoma | 0 to 6 days | Unilateral* Pain
* Redness
* Swelling
* Pain with eye movement
 | * Proptosis
* Eyelid edema
* conjunctival injection and chemosis
 | CT* Proptosis
* Scleral wall thickening
* Orbital fat haziness

B-scan* Thick posterior ocular wall
* T-sign
 | LogMAR 0 | Systemic NSAID | Complete resolution in 4-14 days |
| Chehade *et al* (2019) (34)  | F | 65 | Osteoporosis | 8 days | Unilateral * Periorbital swelling
* Headaches
* Vertical diplopia
 | * Periorbital edema
* Conjunctival injection and chemosis
* Proptosis
* Restriction of extraocular muscles
* Anterior chamber cells, flare and fine keratic percipitates
 | MRI* Intra-orbital fat stranding
* Enhancement of optic nerve sheath, sclera and periorbital soft tissue
 | 6/7.5 | Topical steroid Ibuprofen  | Complete resolution after 5 weeks |
| Herrera *et al* (2019) (35)  | F | 56 | Osteoporosis  | 1 day | Unilateral* Periorbital swelling
* Pain with eye movement
* tearing
 | * Lid edema
* Restriction of extraocular movement
* Conjunctival chemosis
 | MRI* Orbital soft tissue thickening
* Enhancement in the intraconal space, along the optic nerve sheath and the retro-orbital sclera
 | 20/25-2 | Oral prednisone  | Complete resolution after 1 week |
| Tan *et al*(2019) (36) | M | 56 | Maintaining bone health in Multiple myeloma | 3 days | Bilateral* Pain
* Lid swelling
* Watery discharge
* Mild decree visual acuity
* Vertical diplopia
 | * Periorbital edema
* Conjunctival injection
 | MRI* Bilateral pre-septal and post-septal soft tissue enhancement
 | N/A | IV methylprednisolone (1mg/kg/day) followed by oral prednisone taper  | Improvement in periorbital edema and pain within 24 hoursPatient needed slow prednisone taper over 2 months due to recurrence of swelling with faster taper |
| Han *et al*(2020) (37)  | F | 59 | Osteoporosis | 2 days | Unilateral* Lid swelling and redness
* Retroorbital pain
* photophobia
* Pain with eye movements
* Diplopia in all gaze positions except primary
 | * Periorbital swelling
* 4 mm proptosis
* Restriction of extraocular muscle movement in all directions
* Lid tenderness and redness
* Conjunctival chemosis
* Normal fundus
 | CT* Pre-septal edema
* Retro-orbital fat stranding
 | 6/6 | IV methyl prednisolone 500 mg x 1 dayFollowed by oral prednisone | Significant resolution in 2 weeks |
| Gupta *et al*(2020) (38)  | F | 66 | Osteoporosis | 3 days | Unilateral* Redness
* Pain with eye movement
 | * Conjunctival injection
* Anterior chamber cells and flare
* Fibrinous exudate
* Keratic precipitates
* Normal fundus
 | None | 20/120 | Topical prednisolone 8x per dayAtropine TID | Complete resolution in 20 days |
| Anandasayanan *et al*(2020) (39)   | F | 75 | Osteoporosis | Within 24 hours | Unilateral* Redness
* Pain
* Blurry vision
* Photophobia
 | * Hyperemic conjunctiva
* Keratic precipitates
* Cells and flare in the anterior chamber
* Normal fundus
 | None | 6/9  | Topical prednisolone | Complete resolution in 2 weeks |
| Khalid *et al*(2021) (40)  | M | 62 | Metastatic prostate cancer – pulmonary and skeletal metastases | 3 days | Unilateral* Redness
* Periorbital discomfort
* Pain with eye movement
 | * Ptosis
* Conjunctival injection and chemosis
* Mild limitation of extraocular muscle movements in all directions
* 2 mm proptosis
 | CT orbits* Fat stranding surrounding posterior sclera and within orbital fat
 | 20/20  | prednisone 1 mg/kg | Complete resolution in 1 week |
| Karmiris *et al*(2021) (41)  | F | 50 | Multiple myeloma | Progressive over 5 days | Bilateral * Redness
* Tearing
* Pain
* Blurry vision
 | * Conjunctival chemosis
* Perilimbalinjection
* Cells in the anterior chamber
* Thick fibrous plaque on lens
* Posterior synechiae
* Normal fundus
 | None | OD 6/9 OS HM | IV dexamethasone 20 mg x 3 days (for her chemotherapy)Oral methylprednisolone 16 mg (for her chemotherapy)Topical steroids (dexamethasone) and cycloplegia  | Complete resolution in 17 days |
| Faryal *et al*(2021) (42)  | M | 45 | IgG Kappa Myeloma and bone-related plasmacytoma | 3 days | Unilateral* Pain
* Redness
* Tearing
* Eyelid swelling
* Joint pain
 | * Conjunctival chemosis
* Periorbital edema
 | CT* Proptosis
* Fat stranding in the intraconal fat
* Medial and superior rectus muscle edema
 | 6/9 | IV methyl prednisolone 500 mg daily x 3 daysOral prednisolone60 mg  | Complete resolution in 1 week |
| Jin *et al*(2021) (43)  | 3 F | 65-87 | Osteoporosis | 24-30 hours | 1 Bilateral2 Unilateral * Pain
* Photophobia
* Blurry vision
* Redness
* Myalgia
 | * Conjunctival injection
* Keratic percipitates
* Anterior chamber flare and fibrin (all 3 cases)
 | CT | Range of 0.5-0.8 ratio | Topical steroids and cycloplegia  | Ranged from 2-4weeks |
| Wolpert *et al* (2021) (44)  | F | 61 | Osteoporosis | 1 day following infusion | Unilateral* Pain
* Blurry vision
* Photophobia
 | * Circumlimmbal injection
* Red desaturation
* Proptosis
* Periorbital edema
* Conjunctival chemosis
* Cells and flare in AC
* Normal fundus
 | CT * Proptosis
* Intraconal fat stranding
* Inflame surrounding globe and optic nerve

B-scan* Scleral thickening
 | 6/24 | 1g IV methylprednisoloneOral prednisoneprednisolone 1% eye drops cyclopentolate 1% eye drops | Complete resolution in 1 week |
| Larid *et al* (2022) (45)  | N/A | 77 | Osteoporotic femoral fracture | 2 days | Unilateral | Inflammatory orbitopathyScleritis | MRI* Inflammation of whole left orbital region

OCT* Choroidal folds
 | N/A | N/A | N/A |
| Jakobsen *et al* (2022) (46) | F | 78 | non-small cell lung cancer with bone metastases | 1 day | Unilateral * Discomfort
* Redness
* peri-orbital swelling
* tearing
* Diplopia
 | * Conjunctival injection and chemosis
* Proptosis
* Mild extraocular muscle restriction
* Cells in the anterior chamber
 | MRI * retrobulbar inflammation and scleritis and inflammation along the optic nerve.
 | 20/120 | Oral Prednisone | Complete resolution (time not specified) |
| Kaiser *et al*(2023) (47)  | F | 68 | Ovarian carcinoma and osteoporosis | Within 24 hours | Unilateral* Blurry vision
* Redness
* Pain
 | * Conjunctival Injection and chemosis
* Descemet’s folds
* Non-granulomatous keratoprecipitates
* Fibrinous strands
* Cells in the anterior chamber
* Posterior synechiae
* Iris hyperemia
 | Ultrasound* Vitreal involvement (T-sign)

OCT* Normal
 | 0.25 ratio | Topical steroids and cycloplegiasubconjunctival injection of dexamethasone (4 mg/ml)  | Significant resolution by 2 weeks |
| Chacko *et al* (2023) (48)  | F | 64 | HER2 positive breast cancer | 4 days post infusion | Unilateral* Blurry vision
* Redness
* Pain with eye movement
 | * Periorbital swelling
* Conjunctival injection
* Uveitis
 | Ultrasound* Normal
 | N/A | Topical steroids  | Complete resolution by 3 weeks |
| Ankireddypalli *et al*(2023) (49)  | F | 71 | Osteoporosis | 1 day | Bilateral* Pain
* Redness
* Tearing
* blurry vision
* photosensitivity
* floaters
* headaches
 | * Conjunctival injection
* mild corneal endothelial folds
* Anterior chamber cells and flare
* Posterior synechiae
 | None | OD 20/60OS 20/50 | Topical steroid and cycloplegia  | 7 days complete resolution |

Abbreviations: CF= Counting finger; CT= Computed Tomography; MRI= Magnetic Resonance Imaging; HM= Hand motion; IV= Intravenous; N/A= Not available; OD= Right eye; OS= Left eye; OCT= Optical coherence tomography