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Zoledronic Acid Induced Acute Anterior Uveitis ; A Case Series

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Abstract
Patients with myeloma may experience excessive bone resorption as a result of signals that myeloma cells transmit that disrupt cell regulation by activating osteoclasts. Here, we present two cases of anterior uveitis in patients with Multiple Myeloma who received Zoledronic acid for the first time. After receiving Zoledronic acid infusion, both patients with multiple myeloma developed ocular redness and pain associated with periorbital puffiness and headache.

Keywords: Zoledronic Acid, Uveitis, Aqueous Flare

Introduction

An integral step in new bone formation is the avid binding of inorganic pyrophosphate (PPi) to hydroxyapatite crystals found in bone. Nitrogen-containing bisphosphonates such as zoledronate are PPi analogs with a higher binding affinity. These bisphosphonates, therefore, preferentially bind to bone, especially at sites that are being actively remodelled. The bone-bound bisphosphonates are released during the process of bone breakdown by osteoclasts. Once released, the bisphosphonate is then absorbed by osteoclasts. Within the osteoclasts, the bisphosphonate binds to and blocks the activity of farnesyl diphosphate synthase (FPPS). FPPS is an essential intracellular enzyme in the 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase pathway responsible for producing isoprenoid lipids, cholesterol, and other sterols. Inhibition of this pathway prevents the posttranslational modification of small proteins, including guanosine triphosphate binding proteins, which are needed for the activity and survival of osteoclasts. Therefore, the administration of zoledronate increases osteoclast apoptosis, thus reducing bone resorption and loss. Osteoblastic activity and bone formation are not impacted by the use of zoledronate. Hence the use of this agent shifts bone metabolic activity in favour of bone formation, reducing bone loss. This ultimately leads to an increase in bone mass and bone density as bone formation exceeds the resorption[1], In multiple myeloma, zoledronic acid is infused IV at a dose of 3 to 4 mg every three to four weeks[2]. In patients with CrCl less than or equal to 60 mL/min must get a dose reduction; nevertheless, dosing intervals are unaffected[3]. In addition to being dose-independent, body weight, body mass index, or gender had no impact on zoledronic acid clearance. It is intended for both benign and malignant bone problems. Its primary applications are to lessen unfavourable skeletal-related events (SREs) in osteoporosis, Paget's disease, myeloma, and malignancies. It is nephrotoxic and should not be administered to people who have serious renal impairment since it might cause hypocalcemia like other strong anti-resorptive drugs. [4,5,6] For the treatment of bone disease associated with myeloma, pamidronate (Pam) and zoledronic acid (ZA) are often relied on. The use of

Pam and ZA in the supportive treatment of MM patients has shown their capacity to mitigate pain and skeletal difficulties brought on by bone involvement, leading to an improvement in quality of life[7]. Chills, fever, influenza-like symptoms, night sweats, rigors and shivering, generalized musculoskeletal pain, gastrointestinal consequences are some of the symptoms that might appear during an acute phase reaction with onset usually within three days following an infusion, and are self-limiting in 24 to 48 hours. [8, 9] .No cases of iritis, scleritis, uveitis were reported during the clinical trials, however a few cases reported in clinical practise. Here, we describe two patients who developed acute anterior uveitis after administration of Zoledronate.

Case Report I

A 37-year-old lady who was diagnosed to have Multiple Myeloma was started on chemotherapy with, Lenalidomide, Bortezomib and Dexamethasone (RVD) and was given injection Zoledronic acid 4mg once a day as infusion. She started having redness in eyes and joint pain on the 5th day. There was no significant past history of any systemic or ocular illness. On examination,there was no diminution of visual acuity and on anterior segment examination of both eyes there were fine keratic precipitate on endothelium with AC flare & presence of cells along with fibrinous membrane over lens. Intraocular pressure of both eyes were within normal limits. Fundus of both eyes were normal with a normal Cup Disc Ratio. She was diagnosed to have Acute Nongranulomatous Anterior Uveitis in both eyes and was treated with topical steroids and anticholinergics. She was prescribed with antibiotic and anti-inflammatory agents (Moxifloxacin 0.5% + Dexamethasone 0.1% eye drops).The symptoms were recovered within 1 week. Later after a month Injection Zoledronic acid 4 mg intravenous infusion was given during off period of lenalidomide which was uneventful.

Case Report Ii

A 68-year-old male was diagnosed to have multiple myeloma was started on chemotherapy with, Lenalidomide, Bortezomib and Dexamethasone (RVD).. He was given Zoledronic acid 4 mg and after 7 days he developed bilateral periorbital swelling, pain in the right eye associated with headache. On examination right eye had puffiness on the conjunctiva implicating mild congestion with AC cells & flare, analyzing the fundus of right side was found to be hazy and the globe was mildly tender. Intraocular pressure of right eye is 22 and left eye is 20. His Right Eye Uveitis was diagnosed. He was advised with Moxifloxacin 0.5% eye ointment QID for 4 weeks. His condition resolved with best-corrected visual acuity. After a month zoledronic acid 4mg was given for the next 2 consecutive months and he responded well clinically, never experienced recurrence of any similar episodes.

Discussion

Cases of ocular inflammation have involved both nitrogen and non-nitrogen-containing bisphosphonates (including alendronate, etidronate, risedronate, clodronate, pamidronate, and zoledronic acid). [10]The ocular manifestations of bisphosphonates includes conjunctivitis, uveitis, episcleritis, scleritis, and keratitis. The intravenous infusion of zoledronic acid is the most potent and long-acting bisphosphonate currently utilized in therapeutic settings, the acute phase reaction (APR), an adverse effect of zoledronic acid (ZOL) infusion, is characterized by unfavorable ocular events. [11] Non-infectious uveitis is usually initiated by an inflammatory stimulus in which cytokines play a central role. Inflammatory ocular diseases including uveitis are thought to have an imbalance among proinflammatory cytokines such as tumor necrosis factor-a (TNF-a), interferon-c (IFN-c), interleukin-1 (IL-1), and interleukin-6 (IL-6), which regulate the immune system to maintain the inflammatory response. Uveitis has also been characterized by a CD4(+) T-helper 1 cells - mediated inflammation with elevations in IL-2, IFN-a, and lymphotoxin, and has a distinctive cytokine pattern of IL-6, IL-8, IL-13, TNF-a, and IL-2 in aqueous humor. It has been suggested that secretions of bisphosphonates into tears can cause ocular manifestations since the bisphosphonates also secrete interleukins resulting in inflammatory responses in the eye. However, the ocular inflammatory response linked to bisphosphonates frequently develops days after delivery and necessitates stopping the medication. [12] The acute-phase response following the initial infusion of an aminobisphosphonate may be influenced by the activation of γ/T cells and the release of cytokines (interleukin γ) it might stimulate the development of a specific subgroup of T cells. [13]

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After the start of the bisphosphonate, incidence of ocular irritation is 0.08%, symptoms typically appear 24 hours to a few weeks following the commencement of treatment, it is believed that the bloodstream absorption and drug secretion into tears from the lacrimal gland, which irritates the eyes mucous membranes, are secondary causes of bisphosphonate-induced ocular inflammation. [14]When a diagnosis is made, corticosteroids containing therapy should start immediately and be discontinued as soon as possible based on the clinical response.

Conclusion

Anterior Uveitis due to zolendronate has been reported in the literature. Before receiving zoledronate, patients should be made aware of the signs and symptoms of ocular damage. This will allow them to report any uveitis like symptoms to doctors or seek advice from ophthalmologists as soon as they appear. Considering the widespread usage of bisphosphonates, ophthalmologists should also be aware of their possible side effects. Clinicians who are well-aware of this association may be able to identify cases in the future early and provide timely care. Once the diagnosis has been made, corticosteroid-containing therapy should begin right away and be tapered off based on the patient's clinical outcome.Patients may be rechallenged with bisphosphonates when they are in the off week of Lenalidomide in the RVD protocol to lessen the above mentioned complications, however further studies regarding the possible interactions and additive side effects need to be undertaken to improve the clarity.

Reference

1. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. In Mayo Clinic Proceedings 2008 Sep 1 (Vol. 83, No. 9, pp. 1032-1045). Elsevier.
2. Anderson K, Ismaila N, Flynn PJ, Halabi S, Jagannath S, Ogaily MS, Omel J, Raje N, Roodman GD, Yee GC, Kyle RA. Role of bone-modifying agents in multiple myeloma: American Society of Clinical Oncology clinical practice guideline update. American Society of Clinical Oncology.
3. medscape.com
4. Greear EL, Bankole A. Zoledronate. StatPearls Publishing; 2023.
5. Jamil M, Daneshvar A, Nachawati D, El Sharu H, Meysami A. A Rare Presentation of Zoledronate- Induced Systemic Inflammatory Response. Cureus. 2023 Jul 7;15(7).
6. Reid IR, Green JR, Lyles KW, Reid DM, Trechsel U, Hosking DJ, Black DM, Cummings SR, Russell RG, Eriksen EF. Zoledronate. Bone. 2020 Aug 1;137:115390.
7. Reid IR, Gamble GD, Mesenbrink P, Lakatos P, Black DM. Characterization of and Risk Factors for the Acute-Phase Response After Zoledronic Acid. Obstetrical & Gynecological Survey. 2011 Feb 1;66(2):97-9..
8. Tanvetyanon T, Stiff PJ. Management of the adverse effects associated with intravenous bisphosphonates. Annals of Oncology. 2006 Jun 1;17(6):897-907.
9. Kotian P, Boloor A, Sreenivasan S. Study of adverse effect profile of parenteral zoledronic acid in female patients with osteoporosis. Journal of clinical and diagnostic research: JCDR. 2016 Jan;10(1):OC04. Fraunfelder FW, Fraunfelder FT. Bisphosphonates and ocular inflammation. N Engl J Med. 2003;348(12):1187–8.
10. Chartrand NA, Lau CK, Parsons MT, Handlon JJ, Ronquillo YC, Hoopes PC, Moshirfar M. Ocular Side Effects of Bisphosphonates: A Review of Literature. Journal of Ocular Pharmacology and Therapeutics. 2023 Feb 1;39(1):3-16.
11. Dick A. Pathophysiology of uveitis. Acta Ophthalmologica. 2014 Sep;92.
12. Curnow SJ, Murray PI. Inflammatory mediators of uveitis: Cytokines and chemokines. Curr Opin Ophthalmol. 2006;17:532–7.
13. Kunzmann V, Bauer E, Wilhelm M. γ/δ T-cell stimulation by pamidronate. New England Journal of Medicine. 1999 Mar 4;340(9):737-8.
14. Ataallah B, Nania C, Shah N. PSAT188 Keeping An Eye On Bisphosphonates: Drug Induced Uveitis. Journal of the Endocrine Society. 2022 Nov 1;6(Supplement_1):A205.

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