

Osteoarthritis Flare-Up Secondary to Zoledronic Acid Infusion: Case Report

Maisa H Al Kiyumi*, Maryam Al Kiyumi, Amira Al Harrasi, Yaqoub Al Saidi, Hana Al Sumri, Asma Al Shidhani, Sanaa Al Sumri and Abdulaziz Al Mahrezi

Department of Family Medicine and Public Health, Sultan Qaboos University, Sultan Qaboos University Hospital, Oman

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*Corresponding author: Drmaysa@squ.edu.om

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Abstract

Zoledronic acid is routinely prescribed in the treatment of osteoporosis and it is generally well tolerated. In this case report, a female patient without any significant co-morbid conditions developed a flare-up of osteoarthritis, causing severe pain and disability after a single infusion of zoledronic acid was described. After infusion, the patient developed fever with chills, generalized body aches, and severe low back pain. Following this, she developed bilateral knee pain, wrist, and small joint pain in the hands (proximal and distal interphalangeal joints). Septic arthritis, gout arthritis, and systemic infection were ruled out by investigations. Radiography revealed signs of osteoarthritis in the following joints: proximal and distal interphalangeal joints of the hands, trapeziometacarpal joint, patellofemoral, and medial tibiofemoral joint on both sides. Symptomatic treatment and supportive care were required for these patients after other causes of serious systemic illness have been excluded. Healthcare professionals need to be aware of this uncommon adverse effect caused by zoledronic acid infusion.

Keywords: Zoledronic acid, flare-up, osteoarthritis, osteoporosis.

Introduction

Zoledronic acid, a third-generation bisphosphonate, is a routinely prescribed drug nowadays for post-menopausal osteoporosis. Intravenous administration of bisphosphonates is generally preferred because of the better gastrointestinal profile and improved adherence. The drug is also prescribed in the treatment of malignancy-associated hypercalcemia, multiple myeloma, secondary bone metastasis, Paget's disease, and other causes of decreased bone mineralization.¹ A recent meta-analysis of clinical trials involving zoledronic acid had shown that a once-a-year infusion of zoledronic acid improves the density of the bone effectively, and significantly prevents hip and vertebral bone fracture in post-menopausal women.² It works by promoting osteoclast apoptosis and thereby, prevents bone re-absorption. It also has an increased affinity for mineralized bone and high turnover sites.³

Zoledronic acid infusion is usually tolerated well in most patients with osteoporosis. The frequently reported adverse symptoms are fever, arthralgia, myalgia, influenza-like symptoms, and musculoskeletal pain. The occurrence of these acute phase reactions ranges between 10 -30% during the initial infusion of the drug. However, in subsequent infusions, incidence gradually declines.⁴ All these effects are usually self-limited and subside within a few days.

Other rare side effects reported are jawbone osteonecrosis, femur neck bone fracture, arrhythmia, severe eye inflammation such as uveitis, electrolyte abnormalities, and renal impairment. Although these side effects occur in varying frequency, they are commonly reported in patients with cancer.³ In this case report, we describe a case of flare-up of osteoarthritis in a woman treated with zoledronic acid for osteoporosis.

Case Report

A 62-year-old woman visited our outpatient department. She was known to have osteoarthritis, osteoporosis and peptic ulcer disease.

Detailed history revealed menopause as the only strong risk factor associated with her osteoporosis condition. In addition, she had no history of long-term steroid intake nor a family history of hip fractures. She also had not undergone any hormonal replacement therapy. Her medications included calcium 600 mg/ vitamin D 800 IU once daily, and paracetamol when necessary.

Previous radiological investigations and examinations had shown features of osteoarthritis in bilateral knees and in the small joints of the hands with Heberden and Bouchard nodules. A diagnosis of osteoporosis was confirmed with a dual-energy X-ray absorptiometry scan (T score= -3.5) and all the routine baseline investigations were carried out. The patient gave no previous history of oral bisphosphonates use. After the diagnosis of osteoporosis was confirmed, she was initiated on zoledronic acid 5 mg IV infusion. The infusion rate was maintained constant, and the whole process was completed uneventfully. Patient hydration status, renal function test, serum vitamin D and calcium levels were all within the normal range.

However, at around 12 hours post infusion with zoledronic acid, the patient developed fever with chills, generalized body aches, and severe low back pain. The fever and back pain subsided with the use of paracetamol within one day. Following this, the patient then developed bilateral knee pain with swelling that subsided within two to three days. Three days post infusion, the patient started to have severe pain in the bilateral wrist and small joints of the hands (proximal and distal interphalangeal joints). The pain was severe, worsened with time, and associated with swelling, redness and restricted joint movements. The pain score was estimated around nine out of ten. There was no history of morning stiffness or skin rash.

Bilateral hand examination revealed tenderness over the Heberden and Bouchard nodules and hand movements were restricted and painful (Figure 1). On wrist examination, swelling over the medial carpal metacarpal joints, severe tenderness and restriction of movements were found. In addition, right and left knee effusion was present.



A

B

Figure 1: Hands and wrist joints: swelling over the medial carpal metacarpal joints and the Heberden and Bouchard nodules

The laboratory investigations showed normal total leukocyte count, urinalysis, creatinine, transaminase, calcium, phosphorus and uric acid. The C-reactive protein was mildly raised (10 mg/L, ref<5) and the rheumatoid factor was negative. Joint fluid aspiration from the knee and wrist was non-inflammatory.

Post incidence radiological imaging revealed signs of osteoarthritis in the following joints: proximal and distal interphalangeal joints of the hands, trapeziometacarpal joint, and medial tibiofemoral joint on both sides (Figure 2).



A

B

Figure 2: (a) X-ray hands and wrists: reduced joint space with degenerative changes in proximal and distal interphalangeal joints of the hands, and trapeziometacarpal joint. (2) X-ray knee joints: reduced joint space with degenerative changes in the medial tibiofemoral joint on both sides.

A diagnosis of a flare-up of osteoarthritis secondary to zoledronic acid infusion was made. The patient was treated symptomatically with paracetamol and codeine. Her symptoms improved gradually, and it took four to five weeks until a full recovery was achieved.

Discussion

In this case report, a flare-up of osteoarthritis of bilateral knee, wrist and small joints of the hand causing severe pain and disability following the first infusion of zoledronic acid has been described. Zoledronic acid inhibits bone re-absorption very effectively by inhibiting osteoclast proliferation and promoting osteoclast cell death. It has an increased affinity for mineralized bone and high bone turnover sites. Zoledronic acid also increases bone mineralization by promoting osteoblast differentiation.³

Previous studies have documented the effectiveness of the drug in the management of post-menopausal osteoporosis. The HORIZON Pivotal Fracture Trial, a placebo-controlled randomized controlled trial, first documented the evidence of the effectiveness of zoledronic acid. The trial showed that a yearly infusion significantly improved the mineral density and was also very effective in decreasing the risk of fractures in post-menopausal women with osteoporosis.⁴ Another large multi-centre trial comparing zoledronic acid IV infusion with oral alendronate, documented evidence favouring zoledronic acid infusion.⁵ An additional study reported that zoledronic acid-treated patients who had bone biopsies exhibited a less excessive bone re-modelling.⁵ Long-term studies have also reported effectiveness and favourable safety profile to zoledronic acid given once yearly over five years.⁶ A HORIZON fracture recurrent trial, which assessed the effectiveness of zoledronic acid in decreasing the fracture risk, reported that annual infusion of the drug significantly reduced the risk of new fractures and was associated with an increased survival rate.⁷

Zoledronic acid, in general, is well tolerated by most patients.⁸ There are some common side effects associated with it, such as fever with chills, myalgia, arthralgia and fatigue, commonly known as acute phase response (APR).^{3,4,9} Among the acute phase response, fever was the most commonly reported symptom (16.1%), followed by myalgia (9.5%), flu-like symptoms (7.8%), headache (7.1%), and arthralgia (6.3%).⁴ The occurrence of APR gradually declined from 30% after the first infusion of zoledronic acid to 2.8% after the third infusion. Although these acute phase symptoms can happen anytime following the infusion of zoledronic acid, most of these symptoms have been reported within 48 hours after the administration of the drug. Most of these effects are often self-limited and they usually disappear within a few days of infusion.⁹ However, some serious adverse effects following zoledronic acid

infusion have also been reported requiring urgent hospitalization and prolonged care, especially in older individuals with multiple co-morbidity, and cancer patients.¹⁰

Moreover, zoledronic acid infusion causing severe musculoskeletal side effects, including the onset of new arthritis and flare-up of existing osteoarthritis causing hospitalization and continuum of care has been reported in two previous studies^{11,12} (Table.1). Werner et al., in a similar case report, described a flare-up of osteoarthritis of both hands after a single infusion of zoledronic acid for osteoporosis. The patient was treated with NSAID and steroids. However, after the second infusion, the patient had only milder symptoms of shorter duration.¹¹ Similarly, White et al. described a patient who developed a flare-up of osteoarthritis of the hand, wrist, ankle and foot, causing significant disability requiring long-term care and physiotherapy after a single dose of zoledronic acid infusion.¹² However, both patients in those case reports had significant co-morbid conditions.

Table 1: Summary of case reports of osteoarthritis flare-ups following zoledronic acid infusion.

Author	Country	Comorbidities	Zoledronic acid dose and indication	Osteoarthritis flare-up site	Symptoms onset	Symptoms resolution time	Flare-up management
Werner de Castro GR ¹¹	Brazil	Osteoporosis, osteoarthritis,	-Zoledronic acid 5 mg I.V. -Treatment of osteoporosis	Interphalangeal and trapeziometacarpal joints of both hands	One day after I.V zoledronic acid	3 days with medications	paracetamol 3g/day Aceclofenac 200 mg/day intramuscular corticosteroid (betamethasone phosphate 2 mg plus betamethasone dipropionate 5 mg)
White SL ¹²	UK	Ischaemic heart disease, hypertension, type 2 diabetes mellitus, atrial fibrillation and a previous pulmonary embolism, osteoporosis, osteoarthritis,	-Zoledronic acid 5 mg I.V. -Treatment of osteoporosis	hands, wrists, ankles and feet	12 hours after I.V zoledronic acid	After 14 days in hospital, she was discharged home with intermediate care services to support personal care, meal preparation and provide further physiotherapy	codeine phosphate buprenorphine tramadol

In general, in addition to musculoskeletal side effects, several other complications have also been reported with zoledronic acid infusion. Ocular complications, specifically anterior uveitis causing severe painful red eye and reduced visual acuity, have also been reported.^{8,10} Studies have also reported the occurrence of renal impairment, which ranges in severity from mild to severe, requiring renal replacement therapies.^{6,8} Hypocalcaemia is another complication seen in some patients after the administration of zoledronic acid infusion. The HORIZON trial reported an incidence of 2.3% of hypocalcaemia; however, most of the cases were asymptomatic and transient.⁷ Studies have also reported severe cases of hypocalcaemia causing convulsions, but most of those patients had some previous underlying neurological conditions.^{8,10} Pseudo-gout attack post zoledronic acid infusion has also been reported.¹³

Interestingly, most of the reactions were not dose dependent, and serious adverse effects have also been reported even in low doses of zoledronic acid infusion for the treatment of osteoporosis. Hence, predicting the incidence of serious adverse effects secondary to zoledronic acid infusion is often challenging.^{10,11} An inflammatory pathway causing activation of the T-cell and subsequent release of cytokines, such as TNF α , IFN γ , and IL-6 has been proposed as the causal factor for the development of acute phase reactions following zoledronic acid infusion. Farnesyl diphosphate FPP enzymes in the mevalonate pathway of cholesterol synthesis have been specifically inhibited by the zoledronic acid. Inhibition of this enzyme causes disruption of the cell signal and osteoclast activation is prohibited. This causes cell apoptosis causing T-cell activation and subsequent release of cytokines causing acute phase reactions.¹⁴ Statins, in theory, which also interrupt the cholesterol mevalonate pathway, can attenuate the acute phase reactions caused by zoledronic acid, although conclusive evidence is not yet available.¹⁵

Conclusion

This case report describes a patient with osteoporosis without any significant co-morbidity, who developed a flare-up of an existing osteoarthritis, causing severe pain and disability following a single infusion of zoledronic acid. Symptomatic treatment and supportive care are required for these patients, excluding other causes of serious systemic illness.

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