Severe polyarthritis secondary to zolendronic acid: a case report and literature review

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Summary

Intravenous zolendronic acid is an established anti-resorptive treatment for post-menopausal osteoporosis and is usually well tolerated. Common side effects, including the classical ‘acute phase response’, are consented for prior to treatment. However, rare but serious adverse reactions to zolendronic acid have been described. We report the case of an older patient with osteoporosis and osteoarthritis who presented within 12 hours of her first zolendronic acid infusion with evidence of a severe acute polyarthritis affecting her peripheral appendicular skeleton, in joints affected by pre-existing osteoarthritis. Despite the prevalence of osteoarthritis, this is the most severe case of polyarthritis following intravenous zolendronic acid to date and only the second reported case. We remind prescribing physicians treating patients with intravenous bisphosphonates, to bear in mind possible rare serious adverse reactions as well as common benign side effects. We postulate age-associated frailty may reduce tolerability to even milder acute phase reactions.

KEY WORDS: zolendronic acid; osteoporosis; acute phase reaction; polyarthritis.

Introduction

Bisphosphonates bind to hydroxyapatite crystals in bone and, having been taken up by osteoclasts, act to reduce bone resorption, attenuating declines in bone mineral density (BMD) (1, 2). Bisphosphonates are the most commonly prescribed anti-resorptive in the management of osteoporosis, reducing the incidence of fragility fractures and associated mortality and morbidity (3-5), as well as being widely used in the management of metabolic and malignant bone disease (6, 7). Zolendronic acid, the most potent bisphosphonate in clinical use due to its high affinity for bone, is given as an annual intravenous infusion for osteoporosis (8). Whilst zolendronic acid is generally well tolerated common side effects include pyrexia, myalgia, arthralgia and fatigue, commonly referred to as acute phase response (APR) symptoms (3, 4, 9). APR symptoms are usually mild and transient (9, 10). However, serious adverse events following zolendronic acid have been reported, often requiring complex medical intervention (11-19). In this report we expand the literature regarding adverse reactions, describing how a frail older patient with multiple co-morbidities developed an acute and severely debilitating reaction to zolendronic acid necessitating prolonged hospital admission. This is only the second case reported of an acute polyarthritis following zolendronic acid infusion, but is the most severe to date (11). Both common benign and rare serious side effects are consented for before commencing zolendronic acid. We suggest in frailer individuals, with poor physiological reserves, the capacity to tolerate even common mild APR reactions may be reduced and this should be considered by prescribing physicians.

Case report

We report an 81-year-old woman with a history of osteoarthritis (OA) and osteoporosis with recurrent falls, also affected by ischaemic heart disease, hypertension, type II diabetes mellitus, persistent atrial fibrillation and a previous pulmonary embolism, for which she took warfarin, amiodarone 100mg daily, diltiazem slow release 240mg daily, ramipril 5mg daily, furosemide 40mg daily and gliclazide modified release (MR) 30mg daily. She took omeprazole 40mg daily for a hiatus hernia and her OA pain was controlled by paracetamol 4g daily, tramadol modified release (MR) 150mg daily and a buprenorphine patch 20micrograms/hour. She also took adcal-D3 and had a history of diabetes mellitus, persistent atrial fibrillation and a previous episode of acute pancreatitis. She lived independently, alone in a bungalow, without additional support and mobilised well with a rollator frame inside and outside the house.

She had been under follow-up for over 10 years for her osteoporosis and extensive osteoarthritis. Radiological imaging over the preceding decade revealed widespread os-
The patient's primary risk factor for osteoporosis was an early menopause (aged 43) following hysterectomy and bilateral salpingo-oophorectomy, with subsequent intolerance of hormone replacement therapy. Otherwise, she had never smoked, drank no alcohol, had normal dietary habits and had no family history of hip fracture, although her mother suffered with Paget’s disease. Her asthma had only required on average one to two short courses of glucocorticoid treatment per year. Over the preceding decade she had lost 5 inches in height and had developed a prominent thoracic kyphosis and lumbar kyphoscoliosis. She experienced chronic back pain for which she took multiple analgesics. Whilst spinal X-rays 13 years following menopause (aged 56 years) had shown no vertebral fractures, repeat imaging aged 80, showed wedging of the lower thoracic and lumbar vertebral bodies (T11, L2, L3, L4). However, these were her

Table 1 - Serial Hologic dual energy X-ray absorptiometry measurements of Bone Mineral Density.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Spine L1-L4 BMD g/cm²</th>
<th>Femoral Neck BMD g/cm²</th>
<th>Forearm BMD g/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>0.962</td>
<td>0.884</td>
<td>n/a</td>
</tr>
<tr>
<td>73</td>
<td>1.036</td>
<td>0.819</td>
<td>0.405</td>
</tr>
<tr>
<td>81</td>
<td>1.000</td>
<td>0.764</td>
<td>0.382</td>
</tr>
<tr>
<td>T-score</td>
<td>-0.8</td>
<td>-0.11</td>
<td>n/a</td>
</tr>
<tr>
<td>65</td>
<td>0.8</td>
<td>0.3</td>
<td>-3.1</td>
</tr>
<tr>
<td>73</td>
<td>-0.4</td>
<td>-0.8</td>
<td>-3.6</td>
</tr>
</tbody>
</table>

After a premature menopause at 43, 3 DXA’s were performed at ages 65, 72, 81 years. When degenerative changes in the lumbar spine lead to artefactual elevations in BMD, BMD was assessed at the right forearm. n/a = not available
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only fragility fractures. The results of serial hologic dual energy X-ray absorptiometry (DXA) scans are shown (Table 1). The patient had previously been unable to tolerate oral bisphosphonates including etidronate, alendronate, risedronate and ibandronate because of recurrent gastrointestinal side effects due to her hiatus hernia. Previous pulmonary embolus precluded use of Strontium Ranelate. Hence, intravenous bisphosphonate treatment with Zolendronic acid was recommended. She was consented within a specialist clinic and given a patient information leaflet with an extensive list of possible common and uncommon side effects. Prior to treatment renal impairment (eGFR 66ml/min), vitamin D deficiency (98nmol/L), hypocalcaemia, multiple myeloma, autoimmune disorders and thyroid dysfunction were excluded.

She received zolendronate (5mg) intravenously over one hour. She awoke later that night with severe arthralgia particularly in her hands, wrists, ankles and feet. Whilst attempting to mobilise out of bed she fell and pain prevented her from rising again unaided. She pulled her ‘Lifeline’ to summon help. On admission to hospital she was pyrexial (37.8 °C) and haemodynamically stable. Examination revealed widespread joint erythema and mild effusions predominantly affecting distal joints including wrists, ankles and the interphalangeal and metacarpophalangeal joints of her hands and feet; knees were affected to a lesser extent. These joints were warm and painful on both active and passive movements. Pain prevented her from standing or even rolling over in bed. Her spine was unaffected. Other system examinations were unremarkable with no identifiable sources of sepsis. Inflammatory markers were raised (White Cell Count 11.5x10^9/L, neutrophils 10.7x10^9/L, C-reactive protein 163mg/L). International Normalised Ratio on admission was 3.0 and peaked at 7.2 on day 2 of this acute inflammatory response. On admission corrected calcium was 2.23 mg/L, phosphate 1.1mg/L, renal and liver function tests and glucose were all normal. Chest X-ray and urine culture were managed within an out-patient setting. In contrast, the severity of reaction we describe here is the most marked to date, with a significant systemic inflammatory response including elevated inflammatory markers, fever and deranged clotting, and is the first to necessitate hospitalisation and intensive physiotherapy to overcome persisting functional impairment. Furthermore, ours is only the second case of a severe polyarthitis in a patient with pre-existing osteoarthritis following zolendronic acid therapy (11). Understandably our patient refused further treatment with zolendronic acid, contrary to low refusal rates observed following milder APR reactions (9).

Bisphosphonates are synthetic analogues of pyrophosphate, an endogenous regulator of bone mineralization. Patient compliance with oral bisphosphonate formulations is generally poor due to complicated administration regimes and common gastrointestinal side effects, notably oesophagitis (25). After one year approximately only 35-45% of patients remains compliant with treatment (26). Zolendronic acid has a unique chemical structure giving it a high affinity for bone, from which it is slowly released, hence only requiring annual administration (4, 8). Avoidance of direct gastric irritation is an additional advantage. Zolendronic acid is usually well tolerated; APR, the most common side effect, comprises a variety of symptoms including fever, chills, myalgia, arthralgia and fatigue. The HORIZON-Pivotal Fracture Trial, the largest phase III trial of zolendronic acid in post-menopausal women with osteoporosis, reported frequencies of fever 16.1%, myalgia 9.5%, flu-like symptoms 7.8%, headache 7.1% and arthralgia 6.3% (4). The occurrence of APR declined with subsequent infusions, with 30% affected by their first infusion but only 2.8% after their third. Following first zolendronic acid infusion 90% (n=1636) rated their APR symptoms as mild or moderate with 10% reporting a severe APR reaction, components of which included fever, musculoskeletal, gastrointestinal, eye and general symptoms (9). Interestingly, 12% (n=770) of those experiencing musculoskeletal side effects rated these as severe, compared to 4% (n=180) of those who received placebo (p<0.0001) (9). APR symptoms were self-limiting with a median duration of 3 days and rarely resulted in treatment discontinuation; hospitalisation was not recorded (9). It is unclear whether prior oral bisphosphonate use reduces the occurrence of post Zolendronic acid APR (9, 27). In addition to musculoskeletal reactions, other serious adverse re-

Discussion
We have described the case of a frail older patient who developed a severe musculoskeletal adverse reaction following her first intravenous infusion of zolendronic acid, presenting as a debilitating polyarthitis predominantly affecting distal joints with established osteoarthritis causing a two week period of immobility and disordered warfarin therapy. Adverse musculoskeletal reactions following treatment with oral bisphosphonates have been reported, including both acute and delayed onset of painful joints, synovitis and development of arthritis in structurally normal joints (20-23) (Table 2). These reactions have typically been self-limiting, not requiring hospitalisation or aggressive medical intervention. Musculoskeletal side effects following intravenous zolendronic acid, have also been reported, including the onset of new arthritis, painful joints and flare of existing osteoarthritis (11, 18, 24). Whilst causing disruption of activities of daily living (ADLs), these cases have been able to be managed within an out-patient setting. In contrast, the severity of reaction we describe here is the most marked to date, with a significant systemic inflammatory response including elevated inflammatory markers, fever and deranged clotting, and is the first to necessitate hospitalisation and intensive physiotherapy to overcome persisting functional impairment. Furthermore, ours is only the second case of a severe polyarthitis in a patient with pre-existing osteoarthritis following zolendronic acid therapy (11). Understandably our patient refused further treatment with zolendronic acid, contrary to low refusal rates observed following milder APR reactions (9).
actions reported include: (i) ocular complications, particularly anterior uveitis, presenting with painful red eyes, chemosis and reduced visual acuity (14, 17, 28) requiring a range of treatments including surgery. However, the role of pre-existing eye disease is not clear. (ii) Renal dysfunction; although not reported in the HORIZON-Pivotal Fracture Trial, recent studies have reported significant acute renal impairment following intravenous zolendronic acid, which can progress to chronic renal impairment, with necessity for renal dialysis (16, 19, 29). High dose infusions, rapid infusion speed and pre-existing renal dysfunction increase the risk of renal deterioration (8, 10, 16). (iii) Hypocalcaemia; zolendronic acid is a potent osteoclast inhibitor. In the HORIZON trial 2.3% of the zolendronic acid treatment group developed mild hypocalcaemia up to 11 days post infusion but all were asymptomatic and hypocalcaemia was transient (4). However, cases of zolendronic acid associated to severe hypocalcaemia leading to seizures have recently been reported (13, 30); although, in these cases there was often an underlying neurodegenerative condition or previous diagnosis of epilepsy. Serious adverse reactions following zolendronic acid are not dose dependent; severe side effects have occurred following both low dose infusions in patients with osteoporosis (11, 13, 15) as well as higher dose infusions in oncological settings (12, 14, 16-19, 24). Defining the characteristics predictive of susceptibility is difficult. Molecular studies have implicated

<table>
<thead>
<tr>
<th>Potential Adverse Reaction</th>
<th>Estimated frequency</th>
<th>Symptom onset post infusion</th>
<th>Indication for Zol</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>APR</td>
<td>APR in 42% after Zol vs APR in 11.7% after placebo b Severe APR in 10% after Zol vs severe APR in 4% after placebo b</td>
<td>≤ 24 hrs</td>
<td>OP (n=7765)</td>
<td>(9)</td>
</tr>
<tr>
<td></td>
<td>APR in 54.9% after Zol</td>
<td>≤ 48 hrs</td>
<td>OP (n=51)</td>
<td>(27)</td>
</tr>
<tr>
<td>Severe MSK side effects a</td>
<td>Case report</td>
<td>≤ 24 hrs</td>
<td>Metastatic breast cancer</td>
<td>(11)</td>
</tr>
<tr>
<td></td>
<td>Case report</td>
<td>≤ 24 hrs</td>
<td>Bone pain secondary to MGUS</td>
<td>(14)</td>
</tr>
<tr>
<td></td>
<td>Case report</td>
<td>≤ 48 hrs</td>
<td>Hormone responsive breast cancer</td>
<td>(28)</td>
</tr>
<tr>
<td></td>
<td>Case report</td>
<td>≤ 48 hrs</td>
<td>Metastatic prostate cancer</td>
<td>(44)</td>
</tr>
<tr>
<td></td>
<td>Case report</td>
<td>≤ 24 hrs</td>
<td>Metastatic breast cancer</td>
<td>(43)</td>
</tr>
<tr>
<td>Anterior uveitis</td>
<td>Case report</td>
<td>≤ 24 hrs</td>
<td>Metastatic breast cancer</td>
<td>(17)</td>
</tr>
<tr>
<td></td>
<td>Case report</td>
<td>≤ 48 hrs</td>
<td>Bone pain secondary to MGUS</td>
<td>(14)</td>
</tr>
<tr>
<td></td>
<td>Case report</td>
<td>≤ 48 hrs</td>
<td>Hormone responsive breast cancer</td>
<td>(28)</td>
</tr>
<tr>
<td></td>
<td>Case report</td>
<td>≤ 48 hrs</td>
<td>Metastatic prostate cancer</td>
<td>(44)</td>
</tr>
<tr>
<td></td>
<td>Case report</td>
<td>≤ 24 hrs</td>
<td>Metastatic breast cancer</td>
<td>(43)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>1.3% with Zol</td>
<td>1-30 days</td>
<td>OP (n=7765)</td>
<td>(4)</td>
</tr>
<tr>
<td></td>
<td>0.4% with placebo b</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Transient increase in creatinine, returned to baseline in 85% by 30 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Case report</td>
<td>≥ 12 months</td>
<td>Multiple myeloma</td>
<td>(19)</td>
</tr>
<tr>
<td></td>
<td>7 cases</td>
<td>1-120 days</td>
<td>Myeloma or metastatic cancer</td>
<td>(16)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.3% with Zol</td>
<td>≥ 30 days</td>
<td>OP (n=7765)</td>
<td>(4)</td>
</tr>
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<td></td>
<td>0.6% with placebo b</td>
<td></td>
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<td>Lip ulceration</td>
<td>Case report</td>
<td>10 months</td>
<td>Metastatic breast cancer</td>
<td>(12)</td>
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<tr>
<td>Seizures secondary to hypocalcaemia</td>
<td>3 case reports</td>
<td>≤ 24 hrs</td>
<td>OP</td>
<td>(13)</td>
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<tr>
<td></td>
<td>Case report</td>
<td>Unknown</td>
<td>Metastatic prostate cancer</td>
<td>(30)</td>
</tr>
<tr>
<td>Tumour lysis syndrome</td>
<td>Case report</td>
<td>Day 4 of daily Zol regime</td>
<td>Metastatic lung cancer</td>
<td>(45)</td>
</tr>
<tr>
<td>ONJ</td>
<td>1.3% receiving Zol vs 1.8% receiving Denosumab</td>
<td>≤ 6 months on monthly Zol (4mg)</td>
<td>Metastatic cancer (n=5723)</td>
<td>(46)</td>
</tr>
<tr>
<td></td>
<td>Increased cumulative hazard of ONJ with Zol vs Pamidronate b</td>
<td>≥ 48 months</td>
<td>Metastatic cancer (n=252)</td>
<td>(47)</td>
</tr>
<tr>
<td>TTP</td>
<td>Case report</td>
<td>Following 3rd Zol infusion</td>
<td>Metastatic breast cancer</td>
<td>(48)</td>
</tr>
</tbody>
</table>

a Self-reported as severe OR seeking professional medical assessment of symptoms OR receiving medical intervention for symptoms; b p<0.001. Study sample sizes shown as (n); Zol: Zoledronic acid; APR: Acute Phase Response; MSK: Musculoskeletal; OP: Osteoporosis; ONJ: Osteonecrosis of the Jaw; TTP: Thrombotic thrombocytopenic purpura; MGUS: Monoclonal gammopathy of unknown significance; Refs: Reference.
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inflammatory pathways. Nitrogen containing bisphosphonates (alendronic acid, risedronic acid, ibandronic acid, zolendronic acid) specifically inhibit enzymes (farnesyl diphosphate FPP) in the mevalonate pathway of cholesterol synthesis. Inhibition of FPP prevents downstream prenylation of GTPase proteins, which are important for cell signaling and osteoclast activation (1). Whilst osteoclast activity is inhibited disruption of cell signaling and subsequent accumulation of intracellular proteins (isoprenyl diphosphate IPP) is believed to initiate cellular apoptosis and activation of γδ T-cells (31, 32). T-cell activation prompts pro-inflammatory cytokine release, TNFα, IFNy, IL-1b and IL-6) which drives an acute systemic inflammatory response, explaining the systematic APR (32, 33, 27). Interruption of the mevalonate cholesterol pathway, using statins, may attenuate the inflammatory process mediated by bisphosphonates and thus reduce inflammatory side effects although evidence is inconclusive (32-36). Our patient was not on a statin at the time of her zolendronic acid infusion.

Despite the suggestion that bisphosphonate associated adverse effects may be mediated by a systemic inflammatory response, bisphosphonates have been trialed in the treatment of osteoarthritis (OA) and inflammatory conditions including ankylosing spondylitis and rheumatoid arthritis (RA) (37-40). Osteoclast activity is responsible for bone destruction in both RA and sub-chondral bone loss in OA. Bisphosphonate inhibition of osteoclasts is therefore proposed to reduce bone destruction and articular damage in these painful conditions (38, 40). It is also thought bisphosphonates may mediate anti-inflammatory effects in inflammatory arthritides, as demonstrated in ankylosing spondylitis and carrageenan-induced arthritis in animal models (39, 41), although, the anti-inflammatory mechanisms initiated by bisphosphonates in such circumstances are not yet fully understood (41).

Conclusion

We have described the case of an older patient with multiple pre-existing co-morbidities who suffered an acute severe inflammatory response in her osteoarthritic joints following a single treatment with intravenous zolendronic acid, causing severe joint pain, a prolonged hospital admission, loss of functional independence and disordered warfarin therapy. Prescribing physicians starting intravenous bisphosphonate treatment should be aware of rare serious adverse reactions as well as common benign side effects in line with local recommended practice (42). We suggest consideration that frailter older patients, with fewer physiological reserves to cope with external stressors, may be less able to tolerate even mild expected acute phase responses.

References

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