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Prolonged Musculoskeletal Toxicity Following Inadvertent Concurrent Alendronate and Zoledronic Acid Therapy with Sustained Improvement in Bone Mineral Density: A Case Report

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Abstract: ***This case describes a woman in her 70s who experienced prolonged musculoskeletal toxicity following unintentional overlap in bisphosphonate therapy with alendronate and zoledronic acid. On initial presentation, she reported chronic, severe myalgias and fatigue, of greater than six months duration, following a single 5 mg zoledronic acid infusion while concurrently taking 35 mg of alendronate once weekly. One of the most common adverse effects reported for both drugs is musculoskeletal (muscle, joint, and bone) pain, more so for zoledronic acid than alendronate. The degree of severity and duration in this patient raises questions regarding a possible acute phase reaction to zoledronic acid infusion and the impact of concurrent use of two bisphosphonates. Serial dual-energy x-ray absorptiometry (DEXA) scans demonstrated an increase in bone mineral density (BMD) up to two years after bisphosphonate therapy termination. This unique case highlights the importance of careful medication reconciliation during transitions between bisphosphonate therapies to prevent severe adverse reactions while demonstrating the prolonged therapeutic effects of bisphosphonates on bone mineral density.***

Keywords: Osteoporosis, Alendronate, Zoledronic acid, Bisphosphonates, Medication error, Acute phase reaction, Musculoskeletal toxicity, Bone mineral density, DEXA

1. Background

Osteoporosis is characterized by decreased bone mass, decreased strength, and increased fragility, thus increasing fracture risk in affected individuals. DEXA scans measure bone mineral density, which can be utilized to diagnose osteoporosis, evaluate fracture risk, and determine response to therapy [1]. DEXA scans obtain images by scanning fracture-prone areas of the body, commonly the hip and lumbar spine. At these locations, BMD is measured and reported as a T-score, which compares the patient's bone density to a young healthy adult. A T-score between -1.0 and -2.5 is diagnostic of osteopenia, while a T-score of less than -2.5 is diagnostic of osteoporosis [1].

Once osteoporosis is diagnosed, first-line pharmacologic therapy consists of bisphosphonates. These agents inhibit osteoclast-mediated bone resorption, resulting in preservation of bone mass and reduction in fracture risk. The selective action of bisphosphonates is due to their high affinity for mineralized bones. Importantly, oral and intravenous routes of bisphosphonate therapy differ in their affinities. Alendronate sodium oral tablets need to be taken continuously, once daily or once weekly, to maintain efficacy, whereas zoledronic acid intravenous infusions can be done once yearly to maintain an equivalent efficacy [2,3]. Well-known adverse effects of bisphosphonates include flu-like illness, myalgias, arthralgias, esophageal erosions, esophageal perforation, osteonecrosis of the jaw, hypocalcemia, and atypical fractures of the long bones [4,5,7]. Concurrent use of more than one bisphosphonate is not recommended due to increased likelihood and severity of adverse effects.

After bisphosphonate discontinuation, their anti-fracture effects can last months to years. No washout period is required when switching between the two medications, but concurrent use is not recommended. Concurrent use of alendronate and zoledronic acid can increase the likelihood and severity of undesirable side effects including myalgias, arthralgias, headache, hypocalcemia, osteonecrosis of the jaw, and renal impairment [4,5,7]. Combination use of bisphosphonates can modulate inflammatory mediators and have additive effects on bone mineral density. There is limited research on combination therapy which is not supported by long-term safety data [6]. Here we report a case of a woman in her 70s who was transitioned from oral alendronate to intravenous zoledronic acid with a short period of concurrent use.

2. Case Presentation

A female in her 70s presented to the primary care outpatient clinic with concerns for a three-month history of generalized body pain and fatigue, worse in the morning and with prolonged physical activity. The patient reported that her symptoms began shortly after receiving her first 5 mg intravenous infusion of zoledronic acid. In the week

following her infusion, she described her pain as the worst pain she has ever experienced, felt in a diffuse polyarticular distribution. At her clinic visit, she reported mild improvement since that initial week but was continuing to have significant pain. She described herself as being very physically active at baseline but had been unable to complete her daily activities for the past three months due to pain, which had mostly confined her to a recliner.

Physical examination demonstrated a height of 155 cm, weight of 47.2 kg, and BMI of 19.5 kg/m². Her past medical history included hypertension, mixed hyperlipidemia, chronic obstructive pulmonary disease (COPD), chronic low back pain, gout, anxiety, and osteoarthritis. Her medications included acetaminophen-hydrocodone 10mg-325mg oral, as needed, for chronic pain. Social history included a 15-year pack history of smoking tobacco, no alcohol use, and no use of illicit drugs. Family history was notable for myocardial infarction, cerebrovascular accident, diabetes mellitus type II, and breast cancer.

Initial workup of the patient consisted of doing a thorough review of her medical history to determine potential causes of her pain and fatigue. Upon further review, it was determined that the patient was being treated for osteoporosis with oral alendronate 35 mg once weekly by her previous provider. The patient had an initial DEXA scan in August 2018, during which she was determined to not have osteoporosis based on her BMD and T-scores. She started taking oral vitamin D and calcium supplements at that time. She underwent a repeat DEXA scan in May 2021 at which time she was started on oral alendronate 35 mg once weekly. The patient continued taking oral alendronate, vitamin D, and calcium supplementation until her next DEXA scan in September 2023.

Between her scans in May 2021 and September 2023, the patient began seeing a new provider and transitioned care. During her follow-up appointment in September, she was recommended to continue oral alendronate therapy as prescribed for another three years, with a total duration of five years. After the appointment, she was notified of a scheduled zoledronic acid infusion. The patient was unaware of the indications for the infusion but consented and received 5 mg intravenous zoledronic acid in October 2023. Due to an error in communication, the patient received this zoledronic acid infusion while simultaneously taking previously scheduled oral alendronate, resulting in a brief period of bisphosphonate overlap.

In the following week, the patient developed severe joint pain, swelling, and generalized debility, prompting presentation to the emergency department. During her follow-up in December 2023, the patient had slight improvement in her symptoms but was still having moderate to severe joint pain, limiting her daily activities. Upon further review of her records, the patient was notified of the overlap in bisphosphonate therapy. She was then recommended to discontinue all bisphosphonate therapy with continuation of her oral vitamin D and calcium supplements. The table below summarizes the chronological timeline of events.

Table 1: Chronological timeline of events

Date	Event
Aug-18	Initial DEXA scan demonstrated osteopenia; oral calcium and vitamin D supplementation were initiated
May-21	Once-weekly oral alendronate therapy initiated
Sep-23	Follow-up DEXA scan reviewed; recommendation to continue oral alendronate
Oct-23	Zoledronic acid infusion administered with concurrent alendronate
	Severe diffuse musculoskeletal symptoms developed
Dec-23	Medication error identified; oral and intravenous bisphosphonate therapy discontinued
Dec-25	Follow-up DEXA scan showed improved BMD

Due to her ongoing myalgias, other inflammatory conditions were considered such as polymyositis, polymyalgia rheumatica, and rheumatoid arthritis. Laboratory evaluation demonstrated a white blood cell count of 6.5 $\times 10^9$/L, red blood cell count of 4.82 $\times 10^{12}$/L, hemoglobin of 14.6 g/dL, C-reactive protein of 0.4 mg/dL, erythrocyte sedimentation rate of 5 mm/hr, and serum creatinine of 0.9 mg/dL. Additionally, her medications were reviewed, and statin-induced myopathy was ruled out as she was not taking a statin medication. Although she continued to have severe side effects, all her inflammatory markers were within the normal range and no other potential causes for her pain and fatigue could be determined. The patient's symptoms were considered most consistent with a severe acute phase reaction, a known adverse effect of bisphosphonate infusion therapy. Concurrent use of oral alendronate may have been a contributing factor to the severity of her symptoms.

3. Results

Serial DEXA scans from 2018 through 2025 demonstrated changes in bone mineral density at the lumbar spine and hip and the table below summarizes the results.

Table 2: DEXA Measurements of AP Spine and Right Femoral Neck

Year	Age (yrs)	AP Spine (L1–L4) BMD (g/cm²)	T-score	Right Femoral Neck BMD (g/cm²)	T-score
2018	69.1	1.033	-1.2	0.781	-1.8
2021	71.9	1.08	-0.8	0.736	-2.2
2023	74.2	1.085	-0.8	0.756	-2
2025	76.3	1.155	-0.3	0.769	-1.7

Review of the patient's DEXA scans from 2018 to 2025 revealed a notable increase in BMD. The first DEXA scan in 2018 revealed a BMD of 1.033 g/cm2 (L1-L4) and 0.781 g/cm2 (Right Femoral Neck) [Table 2]. Given her T-scores of greater than -2.5, placing her in the osteopenia range, she was initiated on supplemental oral calcium and vitamin D. Repeat DEXA scan in 2021, revealed a mild improvement in BMD to 1.080 g/cm2 (L1-4) but a further decline to 0.736 g/cm2 (Right Femoral Neck) [Table 2]. At that time, she was initiated on bisphosphonate therapy with oral alendronate 35 mg once weekly and continued supplemental calcium and vitamin D.

Repeat DEXA scan in September 2023 was unremarkable for any significant improvement or decline in BMD at the spine or right hip as compared to 2021. The patient remained on the

same oral medications as before with the additional 5 mg intravenous zoledronic acid she received in October 2023.

The patient underwent repeat DEXA scan in December 2025 at which time she had not received oral or intravenous bisphosphonate therapy since December 2023. DEXA results in 2025 revealed a BMD of 1.155 g/cm2 (L1-4) and 0.769 g/cm2 (Right Femoral Neck) [Table 2]. These results demonstrate substantial improvement in BMD, surpassing her 2018 baseline measurements at L1-4 and the Right Femoral Neck with T-scores of -0.3 and -1.7, respectively. While BMD significantly improved at the spine, T-scores at the Right Femoral Neck remained in the osteopenia range without further decline to osteoporosis.

4. Discussion

The most well-known adverse effects associated with oral bisphosphonate therapy include gastrointestinal upset with nausea, dyspepsia, abdominal pain, and gastritis [7]. Approximately 4.1% of patients report musculoskeletal pain with daily oral dosing as compared to 55% of patients with annual intravenous infusions [8]. One of the major adverse effects associated with zoledronic acid is transient acute phase reactions with incidence suggested to be highest with the first infusion and decreased with subsequent doses [7]. Zoledronic acid is a known modulator of IL-6 and TNF-a and can trigger acute phase reactions, defined as flu-like symptoms occurring within three days of the infusion [9]. Zoledronic acid in combination with alendronate increases expression of these cytokines, thus increasing severity of the reaction [6].

The patient's severe and prolonged symptoms were most consistent with an acute phase reaction following zoledronic acid infusion. The concurrent use of alendronate may have contributed to symptom severity, although a direct causal relationship cannot be established. Alternative causes of polyarticular pain and myalgias were considered including medication-induced myopathy, viral infections (including influenza and COVID-19), tick-borne illnesses, and autoimmune conditions such as polymyalgia rheumatica, rheumatoid arthritis, and inflammatory myopathies. These were considered less likely given the chronicity of symptoms, absence of systemic features, lack of relevant exposures, and normal inflammatory and hematologic laboratory studies.

Concurrent use of alendronate and zoledronic acid can increase the likelihood and severity of undesirable side effects including myalgias, arthralgias, headache, hypocalcemia, osteonecrosis of the jaw, and renal impairment [4,5,7]. Zoledronic acid in combination with alendronate has been shown to modulate inflammatory mediators including IL-6 and TNF-α [6]. Given the already increased incidence of musculoskeletal pain reported with intravenous zoledronic acid compared with oral alendronate, concurrent use may have contributed to the severity and prolonged duration of symptoms observed in this patient.

Much of the current research suggests limitation of bisphosphonate therapy to five years to avoid atypical fracture risk. Drug holidays should be considered after this time with continued BMD monitoring with DEXA scans. While there are no definitively established drug holiday timelines, bisphosphonate reinitiation can be considered if monitoring reveals a decline in BMD [7]. Studies comparing long-term efficacy following bisphosphonate discontinuation demonstrated continued suppression of bone turnover markers (BTM) for up to five years following discontinuation of alendronate and three years following discontinuation of zoledronic acid [10]. Additional studies found that individuals who received 4mg of annual zoledronate versus placebo had continued suppression of BTM at 24- and 36-month follow-ups and a higher BMD between 24 to 36 months [11]. The long-term effectiveness of both oral alendronate and intravenous zoledronate as shown by the studies explain the improved BMD seen in our 74-year-old patient, most notably at the spine, L1-4, on repeat DEXA in 2025 [Table 2]. It remains unclear whether the patient's two years of alendronate therapy, single dose of intravenous zoledronic acid, or the brief overlap in bisphosphonate therapies contributed most to her DEXA results.

5. Conclusion

This case report highlights the potential for severe and prolonged musculoskeletal toxicity associated with concurrent bisphosphonate therapy as well as acute phase reactions induced by zoledronic acid. It also reinforces the importance of medication reconciliation during transitions between osteoporosis therapies. . Future research should characterize the risk factors for severe musculoskeletal toxicity after zoledronic acid infusion and determine whether overlapping bisphosphonate exposure increases susceptibility to prolonged adverse reactions. Although sustained improvement in bone mineral density was observed after treatment discontinuation, the relative contribution of each bisphosphonate remains uncertain and warrants further investigation.

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