

SIAN YIK LIM, MD

Bone and Joint Center, Straub Clinic, Honolulu, HI

MARCY B. BOLSTER, MD

Associate Professor of Medicine, Harvard Medical School; Director, Rheumatology Fellowship Training Program, Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Boston, MA



**BRIEF ANSWERS
TO SPECIFIC
CLINICAL
QUESTIONS**

Q: What can we do about musculoskeletal pain from bisphosphonates?

A: Bisphosphonates, especially intravenous zoledronic acid, often cause influenza-like symptoms such as severe musculoskeletal pain, fever, headache, malaise, and fatigue, sometimes accompanied by nausea, vomiting, and diarrhea. As many as 30% of patients experience these symptoms, which are usually transient, last up to 1 week, and, in most patients, only rarely recur with subsequent infusions.

It is essential to counsel and reassure patients about these reactions before starting treatment. We recommend that patients take acetaminophen before intravenous bisphosphonate infusions, and if an acute-phase reaction occurs, we provide adequate supportive care with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs). If patients report severe musculoskeletal pain, then consider discontinuing the bisphosphonate treatment.

■ INFLUENZA-LIKE SYMPTOMS

The acute-phase reaction is a transient inflammatory state characterized by influenza-like symptoms such as fever, myalgia, joint pain, and nausea. It often occurs within the first few days after initial exposure to a bisphosphonate. Patients tend to rate the symptoms as mild to moderate. Symptoms may recur with subsequent doses; however, the incidence rate decreases substantially with each subsequent dose.

With intravenous bisphosphonates

Reid et al¹ analyzed data from a trial in which

7,765 postmenopausal women with osteoporosis were randomized to receive intravenous zoledronic acid or placebo; 42.4% of the zoledronic acid group experienced symptoms that could be attributed to an acute-phase reaction after the first infusion, compared with 11.7% of the placebo group ($P < .0001$). Statistically significant differences ($P < .0001$) in symptoms between the groups included the following:

- Fever 20.3% vs 2.5%
- Musculoskeletal symptoms 19.9% vs 4.7%
- Gastrointestinal symptoms 7.8% vs 2.1%

Of the patients describing musculoskeletal symptoms after receiving zoledronic acid, most (79%) described them as generalized pain or discomfort, while about 25% said they were regional, usually localized to the back, neck, chest, and shoulders, 5% described joint stiffness, and 2.5% reported joint swelling.¹

In this and other studies,¹⁻³ acute-phase reactions most commonly occurred within the first few days after the infusion and were rated as mild to moderate in 90% of cases.^{1,2} Patients who reported an acute-phase reaction were not more likely to opt out of subsequent infusions. The authors postulated that this was most likely because acute-phase reactions were mild and transient, and most resolved within 1 week.¹ The incidence decreased with each subsequent infusion of zoledronic acid¹⁻³; rates of the acute-phase reaction at years 1, 2, and 3 were 30%, 7%, and 3%, respectively.¹

With oral bisphosphonates

The acute-phase reaction is less common with oral bisphosphonates (occurring in 5.6% of patients in a retrospective study⁴) and is usually less severe.^{4,5}

The symptoms, often described by patients as influenza-like, may last up to 1 week

Dr. Bolster has disclosed grant support from AbbVie Pharmaceuticals and remuneration for clinical trial research from Cumberland Pharmaceuticals.

doi:10.3949/ccjm.85a.18005

■ AMINOBISPHOSPHONATES INDUCE INFLAMMATORY CYTOKINES

Musculoskeletal pain related to the acute-phase reaction is thought to be due to transient release of inflammatory cytokines such as interleukin 6, interferon gamma, and tumor necrosis factor alpha from macrophages, monocytes, and gamma-delta T cells.⁶

Bisphosphonates are taken up by osteoclasts and inhibit their function. But bisphosphonates are not all the same: they can be divided into aminobisphosphonates (eg, alendronate, pamidronate, risedronate, zoledronic acid) and nonaminobisphosphonates (eg, clodronate, etidronate).

Inside the osteoclasts, aminobisphosphonates inhibit farnesyl diphosphate synthase in the mevalonate pathways, thus disrupting cell signaling and leading to apoptosis.⁷ However, inhibition of farnesyl diphosphate synthase also increases intracellular levels of isopentyl pyrophosphate, which induces T-cell activation; this is thought to result in release of inflammatory cytokines, leading to the acute-phase reaction.^{7,8}

In contrast, nonaminobisphosphonates such as clodronate and etidronate, after being internalized, are metabolized into nonhydrolyzable adenosine triphosphate, which is toxic to the osteoclast. The acute-phase reaction or influenza-like illness is unique to aminobisphosphonates; nonaminobisphosphonates have not been associated with an acute-phase reaction.

■ TRIALS OF PREVENTIVE TREATMENT

With NSAIDs, acetaminophen

Wark et al⁹ randomized 481 postmenopausal women who had osteopenia but who had never received bisphosphonates to 4 treatment groups:

- Zoledronic acid 5 mg intravenously plus acetaminophen 1,000 mg every 6 hours for 3 days
- Zoledronic acid 5 mg intravenously plus ibuprofen 400 mg every 6 hours for 3 days
- Zoledronic acid 5 mg intravenously plus 2 placebo capsules every 6 hours for 3 days
- Placebo infusion plus 2 placebo capsules every 6 hours for 3 days.

Patients were assessed for fever and wors-

ening symptoms over 3 days after the infusion. The group that got zoledronic acid infusion and placebo capsules had the highest rates of fever (64%) and worsening symptoms (76%); acetaminophen and ibuprofen reduced these rates to an approximately equal extent, to 37% for fever and 46% (acetaminophen) and 49% (ibuprofen) for worsening symptoms. The group that received placebo bisphosphonate infusions had the lowest rates of fever (11%) and worsening symptoms (17%).

Silverman et al¹⁰ found that acetaminophen 650 mg taken 45 minutes before intravenous zoledronic acid infusion and continued every 6 hours for 3 days led to an absolute risk reduction of 21% in the incidence of fever or use of rescue medication compared with placebo.

Trials of other agents

In a study of 60 women,¹¹ 30 received an oral bolus of cholecalciferol 300,000 IU 5 days before zoledronic acid 5 mg infusion plus daily calcium 1,000 mg and vitamin D 800 IU, and 30 received a placebo pill 5 days before the same infusion and vitamin regimen as the other group. The preinfusion oral bolus did not decrease the incidence of acute-phase reactions, although it led to a small decrease in the severity of musculoskeletal pain (the median pain score was reduced from 2 to 1 on a scale of 0 to 10).

Other interventions such as fluvastatin and oral dexamethasone given before intravenous zoledronic acid did not reduce the severity or incidence of the acute-phase reaction.^{10,12,13}

■ OUR APPROACH

Before starting bisphosphonate therapy, patients should be counseled about the possibility of acute musculoskeletal pain and other symptoms of the acute-phase reaction.

For intravenous bisphosphonates

We advise all patients scheduled to receive intravenous bisphosphonates to take acetaminophen 650 to 1,000 mg once on the morning of the infusion. We prefer acetaminophen over NSAIDs for prophylaxis to avoid the gastric mucosal and renal toxicity more common with NSAIDs, especially in the elderly.

If the patient has a history of acute musculoskeletal pain or other symptoms of an acute-

If the acute phase reaction or musculoskeletal pain is severe or persists, discontinue the bisphosphonate

phase reaction after bisphosphonate infusion, we advise a more aggressive approach to prophylaxis: acetaminophen 650 mg 1 hour before the infusion, then every 6 hours for up to 3 days. This approach, with acetaminophen or NSAIDs, has been shown in large randomized controlled trials to reduce the incidence and severity of the acute-phase reaction.

If an acute-phase reaction occurs, we inform patients that the likelihood decreases and is quite low with subsequent doses. We provide correct and honest information, so that patients who experience an acute-phase reaction can make an informed decision about continuing bisphosphonate treatment or switching to another treatment. If the patient decides to continue with intravenous bisphosphonate treatment, we recommend more-aggressive prophylaxis with acetaminophen or NSAIDs with subsequent infusions.

For oral bisphosphonates

We do not prescribe prophylactic treatment with acetaminophen or NSAIDs with oral bisphosphonates, but we do advise patients to take acetaminophen or NSAIDs as needed for mild to moderate musculoskeletal pain, should this occur.

We try to continue treatment in mild to moderate cases, while monitoring the patient closely to see if the musculoskeletal pain resolves within 1 to 2 weeks.

If the pain is severe or does not resolve in 1 to 2 weeks, we offer switching to another drug class. Since musculoskeletal pain with oral bisphosphonates does not represent an allergic reaction, we have switched patients

from oral to intravenous bisphosphonates without recurrence of musculoskeletal pain.

SEVERE MUSCULOSKELETAL PAIN BEYOND THE ACUTE PHASE

Severe musculoskeletal pain that may not be related to the acute-phase reaction, although rare, has been reported.^{5,14} From 1995, when alendronate was approved for osteoporosis, through 2002, the US Food and Drug Administration received reports of severe musculoskeletal pain in 117 patients.¹⁵

This severe musculoskeletal pain related to bisphosphonate use remains poorly characterized. It has been reported to occur days or months (median time 14 days, range same day to 52 months) after starting bisphosphonate therapy and to resolve only if the bisphosphonate is stopped.^{5,15} It differs from typical acute-phase reactions, which tend to occur with the initial dose (intravenous or oral) and resolve within several days. There are case reports of polyarthritis with synovitis that recurred with each bisphosphonate dose (oral or intravenous) and led to discontinuation of the bisphosphonate.^{14,16-18}

Clinicians need to be aware of the possibility of severe musculoskeletal pain and consider stopping bisphosphonate treatment in these cases. Besides discontinuation, acetaminophen, NSAIDs, and, in rare cases, glucocorticoids or short-term opiate therapy may be used for symptom control. In patients with a severe or persistent acute-phase reaction or musculoskeletal pain, discontinuation of bisphosphonates is warranted. ■

REFERENCES

1. Reid IR, Gamble GD, Mesenbrink P, Lakatos P, Black DM. Characterization of and risk factors for the acute-phase response after zoledronic acid. *J Clin Endocrinol Metab* 2010; 95(9):4380-4387. doi:10.1210/jc.2010-0597
2. Black DM, Delmas PD, Eastell R, et al; HORIZON Pivotal Fracture Trial. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007; 356(18):1809-1822. doi:10.1056/NEJMoa067312
3. Lyles KW, Colon-Emeric CS, Magaziner JS, et al; HORIZON Recurrent Fracture Trial. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007; 357(18):1799-1809. doi:10.1056/NEJMoa074941
4. Bock O, Boerst H, Thomasius FE, et al. Common musculoskeletal adverse effects of oral treatment with once weekly alendronate and risedronate in patients with osteoporosis and ways for their prevention. *J Musculoskelet Neuronal Interact* 2007; 7(2):144-148. PMID:17627083
5. US Food and Drug Administration (FDA). Information for healthcare professionals: Bisphosphonates (marketed as Actonel, Actonel+Ca, Aredia, Boniva, Didronel, Fosamax, Fosamax+D, Reclast, Skelid, and Zometa). <https://wayback.archive-it.org/7993/20170722190245/https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124165.htm>. Accessed August 1, 2018.
6. Dicuozzo G, Vincenzi B, Santini D, et al. Fever after zoledronic acid administration is due to increase in TNF-alpha and IL-6. *J Interferon Cytokine Res* 2003; 23(11):649-654. doi:10.1089/10799900332258782
7. Olson K, Van Poznak C. Significance and impact of bisphosphonate-induced acute phase responses. *J Oncol Pharm Pract* 2007; 13(4):223-229. doi:10.1177/1078155207080806
8. Roelofs AJ, Jauhainen M, Monkkinen H, Rogers MJ, Monkkinen J, Thompson K. Peripheral blood monocytes are responsible for gamma delta T cell activation induced by zoledronic acid through accumulation of IPP/DMAPP. *Br J Haematol* 2009; 144(2):245-250. doi:10.1111/j.1365-2141.2008.07435.x

9. **Wark JD, Bensen W, Recknor C, et al.** Treatment with acetaminophen/paracetamol or ibuprofen alleviates post-dose symptoms related to intravenous infusion with zoledronic acid 5 mg. *Osteoporos Int* 2012; 23(2):503–512. doi:10.1007/s00198-011-1563-8
10. **Silverman SL, Kriegman A, Goncalves J, Kianifard F, Carlson T, Leary E.** Effect of acetaminophen and fluvastatin on post-dose symptoms following infusion of zoledronic acid. *Osteoporos Int* 2011; 22(8):2337–2345. doi:10.1007/s00198-010-1448-2
11. **Catalano A, Morabito N, Atteritano M, Basile G, Cucinotta D, Lasco A.** Vitamin D reduces musculoskeletal pain after infusion of zoledronic acid for postmenopausal osteoporosis. *Calcif Tissue Int* 2012; 90(4):279–285. doi:10.1007/s00223-012-9577-6
12. **Thompson K, Keech F, McLernon DJ, et al.** Fluvastatin does not prevent the acute-phase response to intravenous zoledronic acid in post-menopausal women. *Bone* 2011; 49(1):140–145. doi:10.1016/j.bone.2010.10.177
13. **Billington EO, Horne A, Gamble GD, Maslowski K, House M, Reid IR.** Effect of single-dose dexamethasone on acute phase response following zoledronic acid: a randomized controlled trial. *Osteoporos Int* 2017; 28(6):1867–1874. doi:10.1007/s00198-017-3960-0
14. **Ugurlar M.** Alendronate- and risedronate-induced acute polyarthritides. *Osteoporos Int* 2016; 27(11):3383–3385. doi:10.1007/s00198-016-3695-3
15. **Wysowski DK, Chang JT.** Alendronate and risedronate: reports of severe bone, joint, and muscle pain. *Arch Intern Med* 2005; 165(3):346–347. doi:10.1001/archinte.165.3.346-b
16. **Gwynne Jones DP, Savage RL, Highton J.** Alendronate-induced synovitis. *J Rheumatol* 2008; 35(3):537–538. pmid:18203307
17. **Gokkus K, Yazicioglu G, Sagtas E, Uyan A, Aydin AT.** Possible alendronate-induced polyarticular synovitis. *J Postgrad Med* 2016; 62(2):126–128. doi:10.4103/0022-3859.174160
18. **White SL, Jacob A, Gregson C, Bhalla A.** Severe polyarthritides secondary to zoledronic acid: a case report and literature review. *Clin Cases Miner Bone Metab* 2015; 12(1):69–74. doi:10.11138/ccmbm/2015.12.1.069

.....
ADDRESS: Sian Yik Lim, MD, Bone and Joint Center, Straub Clinic, 800 S. King Street, Honolulu, HI 96813; limsianyik@gmail.com