

## Serious Toxicity with a Generic Formula of Zol Acid

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**Abstract:** Intravenous zoledronic acid (ZOL) is an integral component for the management of patients with bone metastases, but can be associated with transient flu-like symptoms, which generally occur only with the first infusion and are typically manageable with non-prescription analgesics. A 50-year-old woman with a bone metastasis secondary to breast cancer received radiation therapy, brand-name ZOL (Zometa®), and letrozole. During the first 3 cycles of Zometa (4 mg every 3-4 weeks), no acute adverse events were reported. For the next 2 cycles she was switched to generic ZOL and experienced severe toxicity (nausea, vomiting, extreme weakness, and incapacitating bone pain) that required hospitalization. Toxicity differences between generic ZOL and Zometa led the patient to pay additional costs for Zometa, and subsequent Zometa infusions were without incident. This is the first case report documenting a clinically significant difference between the safety profiles of a generic formulation of ZOL and brand-name Zometa.

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### 1. Introduction

Continued improvements in therapeutic medicine have resulted in prolonged survival of patients with cancer, and consequently, physicians must manage the long-term complications of cancer and its treatment. Bone metastases are a common complication in patients with a variety of solid tumors [1] and the skeleton is 1 of the 3 most frequent sites of metastasis (including lung, liver, and bone) [2]. All cancers have the potential to metastasize to bone; however, tumors of the breast, prostate, lung, kidney, and thyroid do so most frequently [1]. These tumors show an intense osteotropism and represent approximately 80% of cases of bone metastases. A devastating complication for patients, the development of bone metastases signals that their disease has become incurable. Furthermore, bone metastases can result in potentially debilitating skeletal-related events (SREs) including pathologic fracture, the need for orthopedic surgery to treat or prevent a pathologic fracture, spinal cord compression, severe bone pain requiring radiotherapy, and potentially life-threatening hypercalcemia of malignancy. Treatment of patients with bone metastases should involve a multidisciplinary team of experts, including oncologists, radiation oncologists, and orthopedic surgeons, with the primary goals of relieving pain, improving quality of life, preventing SREs, and restoring functional independence, to minimize the impact on patients' lives. Management options for patients with bone metastases include pharmaceutical agents (eg, bisphosphonates [BPs] and analgesics), radiotherapy, and surgery. These treatments are normally used in combination, depending on the

severity of bone destruction and the life expectancy of the patient. Bisphosphonates inhibit osteoclast-mediated bone resorption and are an integral component of care. Analogues of pyrophosphate, BPs have a high affinity for the mineralized surface of bone and were initially recognized for their ability to reduce bone resorption by inhibiting osteoclasts. However, preclinical studies have demonstrated direct and indirect anticancer activities for some BPs, such as reducing cancer cell proliferation, inducing cancer cell apoptosis, anti-angiogenic effects, and inhibiting cancer cell adhesion and invasion of the extracellular matrix [3]. Additionally, BPs have been shown to reduce bone tumor area in multiple animal models [3]. Moreover, zoledronic acid (ZOL) has demonstrated anticancer benefits in some early breast cancer trials and in other settings, including metastatic disease [4]. Two different types of BPs are currently utilized for treating patients with bone metastases from breast cancer—those that contain nitrogen and those that do not. Those without nitrogen are known as first-generation BPs (eg, clodronate) and inhibit osteoclast-mediated bone resorption mostly via inhibition of mitochondrial ATP. Nitrogen-containing BPs (eg, pamidronate, risedronate, ibandronate, and ZOL) prevent bone resorption by inhibiting farnesyl diphosphate synthase. On the basis of systematic review and meta-analyses of published data from clinical trials of BPs [5,6]. It is clear that BPs reduce SRE risks in patients with metastatic bone disease from breast cancer. Bisphosphonates also reduce bone pain. Furthermore, ZOL has been shown to significantly delay the onset of SREs and reduce the ongoing risk of SREs, supporting initiation of therapy as soon as

bone metastases are diagnosed and continuing until performance status significantly declines [6,7]. To date, the majority of evidence supports the use of the intravenous (IV) nitrogen-containing BP ZOL for preventing SREs in patients with multiple myeloma or bone metastases secondary to any solid tumor[6,8]. when administered intravenously, BPs have been associated with a transient acute-phase reaction including fever, arthralgia, and bone pain (described as “flu-like symptoms”). These reactions generally occur with the first infusion only, are usually self-limiting, resolve within 1 to 2 days of administration, and can typically be managed with nonprescription analgesics [9]. In the majority of patients, reactions are infrequent with subsequent infusions [9]. The underlying cause of the characteristic acute-phase reaction with IV ZOL is believed to be through transient release of cytokines such as tumor necrosis factor alpha and interferon from immune cells and activation of the immune system (eg, V $\gamma$ 9V $\delta$ 2 T cells) against cancer cells [10]. We report here a case study documenting a dramatic difference between the safety profiles of a generic ZOL and the brand-name ZOL formulations.

## 2. Case presentation

A 50-year-old Iranian woman presented in January 2005 with cancer in her right breast (stage IIIa, T3, N2, M0). A Tru-Cut biopsy was performed, revealing poorly differentiated, infiltrating, HER2/Neu-negative ductal carcinoma with vascular permeation and estrogen- and progesterone-receptor strong positive staining in 10% of cells. The patient received 4 cycles of neoadjuvant 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) chemotherapy with good clinical response, followed by right modified radical mastectomy in May 2005. Postmastectomy histopathology revealed multicentric, poorly differentiated, infiltrating ductal carcinoma, with 5 of 10 nodes positive. She received adjuvant therapy with 4 cycles of docetaxel and radiotherapy, followed by sequential endocrine therapy with tamoxifen for approximately 6 months followed by letrozole, beginning in November 2005. In March 2007, after 22 months of adjuvant endocrine therapy and surveillance, the patient reported lower back pain. A bone metastasis was detected in the lumbar spine, for which she received external beam radiotherapy to the lumbar spine and began therapy with the brand-name ZOL (Zometa; 4 mg every 3–4 weeks) plus second-line adjuvant letrozole. She received Zometa for the first 3 cycles with good tolerance, and reported no acute adverse events. As of June 2007, our institution’s policies dictated that she receive generic ZOL for continued monthly BP therapy. On infusion of generic ZOL, the patient experienced extreme weakness, nausea, vomiting (all grade 2, as defined by

[CTCAE]), and incapacitating bone pain (CTCAE grade 3). As a result, the use of weak opioids such as tramadol (50 mg IV every 8 hours) in conjunction with paracetamol (500 mg every 8 hours) was necessary for pain control, and the patient had to be hospitalized for 2 to 3 days of evaluation and monitoring after each of the 2 generic ZOL infusions received. The severity of adverse events experienced by the patient was the same after both the first and second infusions of generic ZOL. Because of the noticeable differences in toxicity profiles between generic ZOL and Zometa, the patient (under her physician’s care) decided to purchase Zometa and assess tolerability. Her subsequent infusion with Zometa was without adverse events. Thereafter, the patient continued therapy with Zometa without complications, and experienced a meaningful reduction in bone pain and improved mobility until eventually succumbing to her disease in February 2009. Written informed consent was obtained from the patient’s family for publication of this case report.

## 3. Discussion

Infusion of IV BPs, including ZOL, is known to be associated with a transient acute-phase reaction (flu-like symptoms) that is generally mild and manageable with nonprescription analgesics. Here we have reported a case in which generic ZOL resulted in hospitalization of the patient because of nausea, vomiting, severe bone pain, and weakness. These debilitating symptoms resulted in increased use of medical resources including nursing care, laboratory tests, and pharmaceuticals including opioids, in addition to standard hospitalization fees. Because the patient had already received Zometa without experiencing these acute complications, it was very likely that the new generic ZOL was responsible for the differences in tolerability. Thus, a return to Zometa confirmed that the original treatment was well tolerated. This suggests that the safety profile of Zometa was better than that of the generic ZOL used in this patient. In the case reported herein, we observed a clear increase in the severity of adverse events associated with the use of generic ZOL. The same phenomenon of increased toxicity with generic ZOL has been observed in numerous other patients at our institution; however, until now it was not possible to make direct comparisons between generic ZOL and Zometa in the same patient. In this case study experience, the generally mild adverse events were amplified so much that the patient required hospitalization after generic ZOL infusion, which is of great concern. Furthermore, although not observed in this case report, we have observed increases in the frequencies of more severe adverse events such as kidney damage and osteone-crosis of the jaw (ONJ) in patients receiving generic ZOL. Interestingly,

according to the package inserts, both the active substance (4 mg ZOL) and inactive ingredients (mannitol, sodium citrate, and sterile water for injection) were the same for the generic ZOL and Zometa formulations. Therefore, the precise reason for the new, acute adverse events experienced after the generic ZOL infusions remains unknown; however, we cannot rule out that patient awareness of the change from Zometa to generic ZOL may have at least contributed to the perceived severity of her symptoms. We believe strongly that before institutions can ethically require the substitution of generic ZOL for Zometa, it will be important to closely monitor and re-evaluate both the efficacy and safety of generic ZOL formulations in patients with bone metastases. Our institutional experience suggests that the generic ZOL used in our patient presents a potential danger to patient safety, perhaps resulting from insufficient manufacturing and/or testing processes. Clearly, more information is needed to validate the safety and efficacy of generic ZOL formulations, and this will be of direct interest to oncologists, but will also have relevance to all healthcare professionals who are confronted by decisions regarding the increasing number of generic drug choices.

#### 4. Conclusion

Those of us who work in healthcare are entrusted with our patients' best interests, and should be highly concerned about the quality and regulation of generic pharmaceuticals such as the emerging formulations of ZOL. Ideally, in the future it will be possible to have international regulatory bodies with the resources and power to monitor and regulate the day-to-day quality of generic medicines, particularly in emerging or developing countries. However, until that time, it is important that treating physicians monitor patients under their care to ensure their safety when new drug formulations are introduced into clinical practice. Although these may be "silent" substitutions enacted by pharmacists, unexpected toxicities, such as those observed in our patient treated with generic ZOL, can alert us to emerging safety concerns. By reporting this case study, we hope to increase vigilance and allow more rapid identification and management of toxicities with substandard ZOL formulations and allow other patients to benefit from our experience.

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