

Risk of atypical femoral fracture with long-term use of alendronate (Bisphosphonates) : A systemic review of literature

Sippy AGARWAL, Saurabh AGARWAL, Priyank GUPTA,
Puneet Kumar AGARWAL, Gunjan AGARWAL, Ankit BANSAL

From Sarojini Naidu Medical College, Agra, India

Several recent reports have described “atypical” fractures of the subtrochanteric and diaphyseal femoral shaft that occur with minimal or no trauma, associated with the use of bisphosphonates. Physicians treating bone diseases with bisphosphonate need, therefore, to be aware of this potential risk and plan the prophylaxis, early diagnosis and prevention of potential consequences. We review the literature on this newly described complication, with particular focus on pathogenesis, preventive measures suggested before and during therapy with bisphosphonates, and the most frequent clinical presentation of these lesions. The recommendations for the management and care of patients who are on long-term use of alendronate (bisphosphonates) are summarized.

Key words : bisphosphonates ; atypical fracture.

INTRODUCTION

Bisphosphonates are a success story ; they have saved thousands of people from the suffering of osteoporotic fractures, without major side effects. They are the most commonly used drugs in the prevention and treatment of osteoporosis, which is a major public health problem and is increasing as the population ages (24).

Alendronate is a potent inhibitor of bone resorption ; it was approved for use in the prevention of osteoporotic fractures by the USA Food and Drug Administration in 1995 (30). Several placebo-

controlled randomized trials have established its effectiveness in preventing bone loss and osteoporotic fractures (9,12,18).

Bisphosphonate can stay in the bone for a prolonged period ; for this reason, the optimal duration of treatment remains uncertain. Despite their excellent safety profile, a number of potential side effects have been identified (1). Other rare but established serious risks include osteonecrosis of the jaw, usually preceded by trauma, infection, or surgery.

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- Sippy Agarwal, MS, Lecturer.
Department of Gynaecology & Obstetrics, Sarojini Naidu Medical College, Agra, India.
 - Saurabh Agarwal, MS, Head of department.
Department of Orthopedics, Maharani Laxmi Bai Medical College, Jhansi, India.
 - Priyank Gupta, MS, Resident.
Department of Orthopedics, Maharani Laxmi Bai Medical College, Jhansi, India.
 - Puneet Kumar Agarwal, MS, General Surgeon.
Himalayan Institute of Medical Sciences, Dehradun, India
 - Gunjan Agarwal, Surgeon.
Obstetrics & Gynaecology, Jaipur, India.
 - Ankit Bansal, MS, Resident.
Sawai Maan Singh Medical College, Jaipur, India.

Correspondence : Dr. Saurabh Agarwal, Department of Orthopedics, Maharani Laxmi Bai Medical College, Jhansi, India.

E mail : drsorabh@rediffmail.com

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Cases of “atypical” fracture of the subtrochanteric and diaphyseal femoral shaft that occur with minimal or no trauma during long-term use of alendronate therapy have been reported in recent literature (13,20). Odvina *et al* (20) reported that long-term alendronate use may cause an increased susceptibility to such fractures. There are now many patients who have been using alendronate for more than five years. The number of patients who have atypical fractures of the femur as a result of prolonged bisphosphonate therapy has recently been increasing (3,7,9,11,14,18,24,26,29).

Literature from the last decade was reviewed using *atypical femoral fracture and long-term use of alendronate (bisphosphonates)* as search terms. Additional articles not obtained in the primary search were identified by assessment of literature referenced in the reviewed articles. Here, we present data on the alarming risk of “atypical” femoral fracture with long-term use of alendronate. Additionally, we have addressed some areas of concern for clinicians and have drawn attention to some currently unresolved issues regarding management and care of patients on long-term bisphosphonate use.

Pathogenesis

Bisphosphonates have a very high affinity for bone mineral, because they bind to hydroxyapatite crystals. Accordingly, bisphosphonate skeletal retention depends on availability of hydroxyapatite binding sites. Bisphosphonates are preferentially incorporated into sites of active bone remodeling, as commonly occurs in conditions characterized by accelerated skeletal turnover. In addition to their ability to inhibit calcification, bisphosphonates inhibit hydroxyapatite breakdown, thereby effectively suppressing bone resorption (23). This fundamental property of bisphosphonates has led to their utility as clinical agents. More recently, it has been suggested that bisphosphonates also function to limit both osteoblast and osteocyte apoptosis (21-22).

It has been shown in experimental animals that alendronate inhibits normal repair of microdamage arising from marked suppression of bone turnover, which, in turn, results in accumulation of microdamage (15-17). A two- to seven-fold increase in

microdamage accumulation after pharmaceutical suppression of bone remodeling was associated with a 20% reduction in bone toughness (the ability to sustain deformation without breaking), without reduction in bone strength (3,16,17). However, the clinical significance of these changes in biomechanical measurements has not yet been well defined.

In addition to microdamage accumulation, chronic over suppression of bone turnover by alendronate may allow secondary mineralization to continue, producing hyper mineralized bone that may be more brittle (2,6,8). The degree of mineralization has been shown to affect the material properties of bone, with low mineralization levels (as seen in osteomalacia) causing reduced stiffness and strength, and hypermineralization likely contributing to reduced fracture toughness (2-8).

Fracture morphology

An unusual type of fatigue fracture of the femoral shaft has been described, which appears to be related to insufficient maintenance remodeling of the bone (9,12,25). The patients have been on bisphosphonates for a long time, and a report by Neviasser *et al* makes it rather clear that these are to blame for this specific type of fracture (18).

These fractures generally affect the proximal third of the femoral shaft but may occur anywhere along the femoral diaphysis. They are usually transverse but may have a shallow, oblique configuration and may be bilateral and associated with a medial spike, cortical thickening, and prodromal symptoms, such as thigh pain (32). The majority of these case reports involved patients receiving long-term alendronate therapy, sometimes together with other antiresorptive drugs, corticosteroids, or proton-pump inhibitors (32).

DISCUSSION

There are many reports of a link between prolonged bisphosphonate therapy and atypical fractures of the femur (2,4,9,13). Osteoporotic fractures typically involve the spine, hip, and wrist, the proximal part of the humerus or tibia, and the pelvis. The proximal femoral diaphysis is not a common localization.

Black *et al* (5) reviewed 284 hip and femur fractures to identify which occurred in the femoral shaft and to assess atypia. They found 12 subtrochanteric or diaphyseal fractures (4%) in 10 patients. The relative hazard ratios for these fractures in patients who were treated with alendronate versus placebo were 1.03 (95% confidence interval [CI], 0.06 to 16.46) in the Fracture Intervention Trial (FIT) study and 1.33 (95% CI, 0.12 to 14.67) in the FIT Long-Term Extension (FLEX) trial. The relative hazard ratio of zoledronate versus placebo was 1.50 (95% CI, 0.25 to 9.00) in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly-Pivotal Fracture Trial (HORIZON-PFT). The authors also concluded that bisphosphonate treatment would result in an annual rate of 2.3 subtrochanteric or diaphyseal fractures per 10,000 patient-years in untreated women with osteoporosis. This rate is consistent with those of the Danish registry study.

Neviaser *et al* (18) looked at all low-energy femoral shaft fractures at their hospital and found that among bisphosphonate users, the stress fractures occurred after a substantially longer treatment than other types of fractures, indicating that the risk of stress fracture increases with treatment time.

In 2008, Visekruna *et al* (31) described severely suppressed bone turnover (SSBT) and atypical skeletal fragility with proximal femoral metadiaphyseal/subtrochanteric fractures in 3 patients on long-term bisphosphonate therapy, all three of whom were receiving another medication (estrogen, glucocorticoid, or raloxifene) that likely further suppressed bone remodeling beyond the effect of the alendronate alone.

Kwek *et al* (12) found an average duration of 5 years versus 6 years in the study of Schilcher and Aspenberg (28). If taken together, these findings suggest that treatment should be stopped after 5 years. It has also been suggested by other authors that bisphosphonate treatment should be terminated after 5 years.

Although most of the reported cases of atypical femoral shaft fracture among bisphosphonate users have occurred in women receiving alendronate (the most commonly used bisphosphonate), similar fractures have also been reported among users of

ibandronate and risedronate (4,15). Furthermore, we found cases of femoral shaft fracture in patients receiving zoledronic acid, as well as in those receiving placebo, so there is no definitive evidence or theoretical reason to believe that any possible increase in risk would be limited to alendronate.

CONCLUSION

Although there is not such magnitude of risk to be panicky but studies are showing a definite association between a dreaded complication of "Atypical" fracture of the subtrochanteric and diaphyseal femoral shaft during long-term use of alendronate that may be an iceberg of disease. So this demands further research to establish causality and determine the exact mechanism which causes this relationship whether it is indeed the accumulation of microdamage due to inadequate remodeling, a change in the elasticity induced brittleness of the underlying bony trabeculae, or some other mechanism.

It is important to raise awareness of the potential for insufficiency fractures in patients on long term, high dose, or intravenous bisphosphonates. There is clearly a need to find a balance between the important benefit of these medications with increased fracture risk. Optimal protocols for the dosage and duration of bisphosphonate therapy and actions to take if a patient has an impending or completed insufficiency fracture while on these medications deserve additional consideration. Their long well time and prolonged suppression of osteoclast activity in the bone can affect fracture healing in some patients months or perhaps even years after discontinuation so that additional steps may be needed to promote fracture healing.

Familiarity with this pattern of clinical history and imaging findings allows the opportunity to recognize the impending fracture risk in patients with insufficiency fractures related to bisphosphonate induced over-suppression of osteoclast-dependent bone remodeling. Knowledge of the potential for low-energy fractures and poor fracture healing in this patient population will facilitate better management to prevent fracture completion and promote healing.

So, on the basis of these initial issues physicians should not rush to judgment and stop prescribing bisphosphonates because of concern about atypical femoral fractures. However, they should be aware and have a warning alarm of the possibility of these rare adverse reactions to the prolonged use of bisphosphonates, and prolonged usage should be reconsidered until long-term safety data are available.

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