Association between alendronate and atypical femur fractures: A meta-analysis

Lu Liu\textsuperscript{a}, Chunyan Li\textsuperscript{a}, Peng Yang\textsuperscript{a}, Jian Zhu\textsuperscript{b}, Dongmei Gan\textsuperscript{c}, Le Bu\textsuperscript{a}, Manna Zhang\textsuperscript{a}, Chunjun Sheng\textsuperscript{a}, Hong Li\textsuperscript{a,*}, Shen Qu\textsuperscript{a}

\textsuperscript{a} Department of Endocrinology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai 200072, China

\textsuperscript{b} Department of Internal Medicine, Shanghai Dachang Hospital, Shanghai 200442, China

\textsuperscript{c} Department of Paediatrics, Ningbo Women and Children's Hospital, Ningbo, Zhejiang Province 315012, China

Abbreviations: ALN, alendronate; AFF, atypical femur fractures.

*Corresponding author at: Department of Endocrinology, Shanghai Tenth People's Hospital, 301 Yanchang Middle Road, Shanghai 200072, China.
E-mail address: lihong_endo@tongji.edu.cn (H. Li); Telephone: 021-66301004.
Abstract

Alendronate (ALN) is a commonly used drug for the treatment of osteoporosis. Atypical femur fractures (AFF) have been associated with long-term use of ALN, and have recently gained considerable attention as ALN use increases. This meta-analysis aimed to detect the relationship between ALN and AFF. The Embase, PubMed, and Cochrane library databases were searched for relevant studies published before Nov 6th, 2014. Studies clearly reporting the relationship between ALN and AFF were selected for our analysis. From these results, the relationship between ALN and AFF was analyzed. Weighted mean differences were calculated using a random-effects model. Five studies were included in this meta-analysis. The results revealed that the use of ALN will not increase the risk of AFF in short term (P > 0.05), and however, there will be a risk of AFF (P < 0.05) with long-term (greater than 5 years) use of ALN. These findings suggest that long-term use of ALN is a risk factor for AFF and more attention should be paid to the clinical applications of ALN.

Keywords

Alendronate; Atypical femur fractures; Meta-analysis; Osteoporosis
**Introduction**

Osteoporosis is a major metabolic bone disease that affects 44 million Americans or 55% of the population 50 years of age or older. Of these, 10 million individuals already have the disease while 34 million more are at increased high risk for osteoporosis (1). Though osteoporosis is often thought of as an older person’s disease, it can strike at any age. The disease causes a significant amount of morbidity and mortality in patients and is often diagnosed after a fracture occurs. Current medications used to treat osteoporosis include bisphosphonates, raloxifene, calcitonin, and hormone replacement therapy (2). Bisphosphonates are a class of widely prescribed drugs that are proven to be effective in reducing common bone fractures in people with osteoporosis and those at high risk of fractures (3-5).

ALN is a potent oral bisphosphonate with a prolonged duration of action and is the most commonly prescribed bisphosphonate (6). The pharmacokinetics of ALN allow for a once weekly regimen that leads to continued maintenance of bone mineral density in months to years after discontinuation (7). ALN could inhibit osteoclast-mediated bone resorption and normalize the rate of bone turnover to premenopausal levels. In both animal and human studies, administration of ALN could increase bone mass and maintain histologically normal bone (8-10). Bone et al. (11) found that clinical symptoms and indicators improved significantly with long-term use of ALN for elderly postmenopausal women with osteoporosis. However, a growing number of recent studies have shown that bone turnover will be suppressed excessively with long-term use of ALN, which will lead to the occurrence of AFF (12).
This study collected relevant literature on the use of ALN and consequent AFF incidence and utilized meta-analysis to clarify the relationship between ALN use and AFF occurrence to provide credible advice for clinicians.

1. Methods

1.1. Literature retrieval

The Cochrane library, PubMed, and Embase databases were searched to retrieve relevant studies published before Nov 6th, 2014. The search criteria “femoral fracture” or “femur fracture” or “hip fracture” or “diaphyseal” or “atypical fractures” and “alendronate” were used in text word searches, while the “related articles” function was used to broaden the search. Reference lists of selected articles were also manually examined to find relevant studies not discovered during the database searches. Any observational or interventional studies that examined the relationship between ALN and AFF were selected. All titles, abstracts, and full papers of potentially relevant studies were assessed for eligibility based on predefined inclusion and exclusion criteria. Eligible papers included studies (1) on the use of ALN and AFF that were published before Nov 6th, 2014; (2) utilizing cohort studies to confirm osteoporosis in a population; (3) where the statistical indicator was AFF. Finally, relevant articles were examined to ensure the diagnosis standards of AFF were consistent. When several reports from the same study were published, only the most recent or informative was included in our meta-analysis. The language was restricted to English.
1.2. Data extraction

Data extractions of all variables and outcomes of interest and assessment of methodological quality were performed independently by 2 readers. Any disagreements were resolved through discussion to reach a consensus. The methodological quality of the trials was evaluated by using the assessment forms from the Agency for Healthcare Research and Quality (AHRQ).

1.3. Statistical analysis

Statistical analysis was performed by using ReviewManager 5.0 software (Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark). Continuous variables were analyzed by using the weighted mean difference. P-values < 0.05 were considered statically significant, and 95% confidence intervals (CIs) were reported. Homogeneity was tested by the Q statistic (significance level at p < 0.10) and the I² statistic (significance level at I² > 50%). If the overall effects of multiple findings were consistent, the fixed-effects model was used; otherwise, the random-effects model was employed. The presence of publication bias was assessed by the visual inspection of a funnel plot.

2. Results

2.1. Literature search

The initial literature search retrieved 1108 relevant articles (duplicates were discarded). Of these 1065 articles were excluded from our analysis for not investigating the topic of interest. The abstracts were reviewed from the 43 remaining articles, and another 38 articles were excluded (2 laboratory or animal studies, 12
reviews, 14 without a control group, and 10 with other bisphosphonates). Therefore, 5 studies matched the selection criteria and were suitable for our meta-analysis (13-17).

A flow-diagram for the selection of studies included in our meta-analysis is shown in Fig. 1. A total of 232,411 patients (53,926 experimental group and 178,485 control group) were included in our analysis. The key characteristics of the included studies are summarized in Table 1. Table 2 summarizes the methodological quality of the studies.

2.2. Main analysis

Fig. 2 summarizes the outcome of our meta-analysis. Heterogeneity analysis was performed on the 5 papers, and the results indicated that heterogeneity was significant (P<0.05, I²=97%). Therefore, the random-effects model was employed. The results showed that: RR = 3.23, 95% CI (0.88, 11.84), P > 0.05 (Fig. 2), and the difference were not statistically significant. Among them, five year oral administration periods were taken in two studies (13, 14), and further stratified studies were performed. Heterogeneity analysis was also performed on these 2 papers, and the results indicated that heterogeneity was fine; therefore, the fixed-effects model was used (P=0.18, I²=44%). The results revealed that RR = 2.55, 95% CI (2.26, 2.88), P < 0.05 (Fig. 3), and the difference was statistically significant. As shown in Fig. 3.

3. Discussion

ALN belongs to the third generation of bisphosphonate drugs that could inhibit the activity of osteoclasts by physicochemically combining with the bone matrix and subsequently blocking the osteoclast process by inducing the secretion of a variety of
cytokines. In addition, ALN can regulate the metabolism of calcium in vivo, prevent the loss of bone mass, and augment bone mineral density; all of which explain why ALN is the most widely used bisphosphonate. Bisphosphonates are the primary agents used to treat osteoporosis, metastatic bone malignancies, Paget disease, multiple myeloma, and hypercalcemia in malignancy. Moreover, bisphosphonates are commonly used for prevention and treatment of a variety of other skeletal conditions, such as low bone density and osteogenesis imperfecta (18, 19).

AFF, the rare adverse reaction resulting from long-term use of ALN, has recently gained more attention from clinicians. Odvina (20) was the first to report AFF from ALN use. He found that spontaneous non-vertebral fractures can occur in patients undergoing long-term use of ALN, even in the absence of obvious initiating trauma. Furthermore, these patients exhibited postoperative fracture delayed union or nonunion. Since then, similar clinical cases were reported in different medical centers (21-23). According to the existing data, the incidence rate of AFF is less than 4‰ in high femoral fractures, and most of the literatures related to AFF were case reports, as shown in Table 3.

Large, randomized, controlled trials have shown that ALN therapy for 3 to 4 years is effective in reducing the risk of both nonvertebral and vertebral fractures in osteoporotic women (16). However, there is considerable controversy over the ideal duration of antiresorptive therapy in light of reports about ALN related AFF. Two randomized trials have been implemented to assess the efficacy of long-term use of ALN and the risk of fractures (24, 25). The results indicated that women are at very
high risk of clinical vertebral fractures when ALN was administered for more than 5 years. However, these trials were conducted in post-menopausal women, and therefore the results may not apply to younger women or to men.

To clarify the relationship between ALN and AFF, and provide credible advice for clinicians, we performed this meta-analysis. The results indicated that ALN administration could not increase the risk of AFF in short term (Lower than 5 years), and however, there will be a risk of AFF (P < 0.05) with long-term (greater than 5 years) use of ALN.

The mechanisms of AFF are still unclear. Allen et al. (26) found that the bone micro-damage caused by ALN increased more than seven fold compared to the control with a concurrent bone mineral density decrease of 40%, leading to increased ease of fracture. Another study also performed by Allen found that the long-term use of ALN could exert adverse effects on bone trabeculae and heterogeneous cross-linking of collagen, which will lead to bone fragility (27). The bone turnover and metabolism of patients with osteoporosis were abnormal, which was the risk factor per se for the occurrence of AFF (28). Some studies have shown that bone turnover could be suppressed excessively with long-term use of ALN, which will lead to excessive accumulation of bone micro-damage and the occurrence of AFF (21). In short, further animal experiments and clinical studies should be performed to clarify the mechanism of AFF.

Considering the potential for the increased risk of AFF, we think that the use of alendronate should not exceed 5 years, and it will be appropriate for patients to
discontinue the use of alendronate after 5 years. Moreover, most of the experts also recommend that the application of ALN should not exceed five years. AFF could heal itself after discontinuation of ALN treatment, but can quickly recur when treatment resumes (23). Teriparatide (recombinant parathyroid peptide) is recommended for patients with AFF. In theory, teriparatide could promote favorable bone metabolism in patients with AFF, however, it is still unclear whether bone mineral density remains unchanged during the teriparatide treatment period, or how long the antiresorptive drugs should be taken (29).

However, our research is not without some deficiency. Of the 5 studies included, 2 were conducted in Denmark, 1 was Taiwanese, while the others were conducted in America, leading to clinical heterogeneity in our study. Moreover, there is little data available regarding the long-term use of ALN and AFF, which may affect our results. In the future, multi-center prospective cohort studies using large sample sizes and various subgroups according to gender and age are needed.

The American Society for Bone and Mineral Research (ASBMR) indicated that physicians should assess each patient’s condition individually because the optimal length of bisphosphonate therapy remains unknown and must be considered on a case-by-case basis (30). Objectively speaking, AFF is the only rare adverse reaction caused by ALN. As such, ALN is still a better option for patients with osteoporosis, and for the majority of patients the benefits outweigh the possible risks. Based on this approach, clinicians should not outright reject ALN, but should pay attention to its application, particularly the duration of administration.
4. Conclusion

In summary, this meta-analysis suggests that patients with long-term use of ALN may develop increased risk of AFF.

Funding

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Declaration of Interests

The authors have declared no conflict of interest.

References


23 Puah KL & Tan MH. Bisphosphonate-associated atypical fracture of the femur: Spontaneous healing with drug holiday and re-appearance after resumed drug


28 Goh SK, Yang KY, Koh JS, Wong MK, Chua SY, Chua DT&Howe TS. Subtrochanteric insufficiency fractures in patients on alendronate therapy: a


34. Sayed-Noor AS, & Sjoden GO. Case reports: two femoral insufficiency fractures


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Figure captions

Fig. 1. Search strategy flow diagram.

Fig. 2. The risk of AFF for patients using ALN.

Fig. 3. The risk of AFF for patients with long-term (≥ 5 years) use of ALN.
Fig. 1. Search strategy flow diagram.
144x180mm (600 x 600 DPI)
Fig. 2. The risk of AFF for patients using ALN.
55x16mm (600 x 600 DPI)
Fig. 3. The risk of AFF for patients with long-term (≥ 5 years) use of ALN.
45x10mm (600 x 600 DPI)
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<thead>
<tr>
<th>Author</th>
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<th>Study design</th>
<th>Female patients (%)</th>
<th>Sample size</th>
<th>Age</th>
<th>AFF number</th>
<th>AFF type</th>
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<tr>
<td>Abrahamsen (13)</td>
<td>1997-2005</td>
<td>Denmark</td>
<td>Corhort study</td>
<td>91.2%</td>
<td>10374</td>
<td>73.1 ± 8.5 vs. 73.1 ± 8.5</td>
<td>76</td>
<td>Trochanter, femoral shaft</td>
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<tr>
<td>Abrahamsen (14)</td>
<td>1996-2005</td>
<td>Denmark</td>
<td>Corhort study</td>
<td>82.8%</td>
<td>158268</td>
<td>69.8 ± 11.6 vs. 69.8 ± 11.6</td>
<td>1049</td>
<td>Trochanter, femoral shaft</td>
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<td>Neviaser (15)</td>
<td>2002-2007</td>
<td>America</td>
<td>Corhort study</td>
<td>84.3%</td>
<td>45 vs. 25</td>
<td>77.1 vs. 69.4</td>
<td>20</td>
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<td>Black (16)</td>
<td>Unknown</td>
<td>America</td>
<td>Corhort study</td>
<td>100%</td>
<td>3223</td>
<td>vs. Unknown 2</td>
<td>2</td>
<td>Trochanter, femoral shaft</td>
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<tr>
<td>Hsiao (17)</td>
<td>2001-2005</td>
<td>Taiwan</td>
<td>Corhort study</td>
<td>Unknown</td>
<td>6159</td>
<td>vs. Unknown 61</td>
<td>61</td>
<td>Trochanter, femoral shaft</td>
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Table 2
The methodological quality of included studies.

<table>
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<tr>
<th>Item</th>
<th>Abrahamsen (13)</th>
<th>Abrahamsen (14)</th>
<th>Andrew (15)</th>
<th>Black (16)</th>
<th>Hsiao (17)</th>
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<tbody>
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<td>1) Define the source of information (survey, record review)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2) List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3) Indicate time period used for identifying patients</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>4) Indicate whether or not subjects were consecutive if not population-based</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5) Indicate if evaluators of subjective components of study were masked to other aspects of the participants</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
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<td>6) Describe any assessments undertaken for quality assurance purposes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>7) Explain any patient exclusions from analysis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>8) Describe how confounding was assessed and/or controlled</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>9) If applicable, explain how missing data were handled in the analysis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>10) Summarise patient response rates and completeness of data collection</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
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<td>11) Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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Table 3

Case studies on atypical femur fractures related with bisphosphonates.

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<tr>
<th>Author</th>
<th>AFF* number</th>
<th>Average treatment time</th>
<th>Average age</th>
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<td>Odvina (31)</td>
<td>7</td>
<td>5.6 (3–8)</td>
<td>60.0 (49–68)</td>
</tr>
<tr>
<td>Goh (28)</td>
<td>9</td>
<td>4.2 (2.5–5)</td>
<td>66.9 (55–82)</td>
</tr>
<tr>
<td>Kwek (32)</td>
<td>26</td>
<td>4.4 (2–10)</td>
<td>66.1 (53–82)</td>
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<td>Lenart (33)</td>
<td>12</td>
<td>7.3 (5.5–9)</td>
<td>70.4 (55–83)</td>
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<tr>
<td>Neviaser (15)</td>
<td>19</td>
<td>6.9</td>
<td>69.5</td>
</tr>
<tr>
<td>Sayed-Noor (34)</td>
<td>2</td>
<td>7.0</td>
<td>72.0</td>
</tr>
<tr>
<td>Aspenberg (35)</td>
<td>2</td>
<td>9.0</td>
<td>57.0</td>
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<tr>
<td>Capeci (2)</td>
<td>14</td>
<td>8.6 (5–13)</td>
<td>61.0 (53–75)</td>
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<td>Sayed-Noor (36)</td>
<td>3</td>
<td>9.0</td>
<td>66.5</td>
</tr>
<tr>
<td>Schneider (37)</td>
<td>3</td>
<td>7.3 (6–9)</td>
<td>63.3 (59–66)</td>
</tr>
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<td>Edwards (12)</td>
<td>2</td>
<td>6.0</td>
<td>60.0</td>
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<td>Koh (38)</td>
<td>16</td>
<td>4.5 (2–7)</td>
<td>68.0 (53–92)</td>
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<tr>
<td>Isaacs (39)</td>
<td>59</td>
<td>7.1 (4–11)</td>
<td>73.7 (67–85)</td>
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