HOW DO BISPHOSPHONATES AFFECT FRACTURE HEALING?

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Abstract

Bisphosphonates (BPs) have been in use for many years for the treatment of osteoporosis, multiple myeloma, Paget's disease, as well as a variety of other diseases in which there is reduced bone mineral density. Given that bisphosphonates inhibit bone resorption, an important stage of fracture healing; this class of compounds has been widely studied in preclinical models regarding their influence on fracture healing. In animal models, bisphosphonate treatment is associated with a larger fracture callus, coincident with a delay in remodeling from primary woven bone to lamellar bone, but there is no delay in formation of the fracture callus. In humans, *de novo* use of bisphosphonate therapy after fracture does not appear to have a significant effect on fracture healing. Rarely, patients with long term use of Bisphosphonates may develop an atypical fracture and delay in fracture healing has been observed. In summary, bisphosphonates appear safe for use in the setting of acute fracture management in the upper and lower extremity in humans. While much remains unknown about the effects on healing of long-term bisphosphonates, use prior to "typical" fracture, in the special case of atypical fracture, evidence suggests that bisphosphonates negatively influence healing.

Keywords

FRACTURE HEALING; BISPHOSPHONATE; DELAYED HEALING; FRACTURE; REVIEW

INTRODUCTION

Bisphosphonates have been in clinical use since 1968 (etidronate), and use of these compounds has increased in prevalence after the Food and Drug Administration approved alendronate for use in September of 1995. As such, millions of doses of bisphosphonates (BPs) have been taken worldwide and we have now begun to collect and analyze critical data regarding acute, as well as long-term consequences of their use. Herein, we will examine the current best evidence regarding the effects of bisphosphonate use on fracture healing, including evidence from animal models, as well as human studies, with the aim to inform the reader about the implications of bisphosphonate use on bone healing.

Fracture repair is a complex, multi-staged process, of which the end goal is the return of the damaged bone to a functional and biomechanically sound state. Immediately post fracture, bleeding occurs and this is followed by the formation of a hematoma at the fracture site.

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This creates an inflammatory environment that recruits mesenchymal stem cells (MSCs) to the site of healing, followed by expansion of these cells and their differentiation into either osteoblasts or chondrocytes. Via intramembranous ossification, the osteoblast cells form new bone on the existing bone surface, flanking the fracture site, generating the hard callus. In the center, over the site of fracture, which is a more hypoxic environment and one that is less mechanically sound, chondrocytes form a cartilaginous or soft callus via endochondral ossification. As the chondrocyte population expands, these cells become hypertrophic and the cartilage tissue is mineralized. The callus is then invaded by the vasculature, allowing for infiltration by osteoclasts that in turn remove the mineralized cartilage allowing for the ultimate bridging of the fracture by woven bone. This is followed by a secondary and more prolonged remodeling phase, which includes resorption by the osteoclasts, which converts the woven bone to lamellar bone, and remodeling of the original fractured bone below the callus, yielding bone that mechanically and anatomically matches the pre-fractured bone.[1, 2]

All Bisphosphonates (BPs) are analogues of inorganic pyrophosphate, wherein a carbon, in place of the natural oxygen, connects the two phosphates. As a result, BPs have two side chains that can be modified to modulate their pharmacological properties. Clinically used BPs can be divided into non-nitrogen containing compounds such as etidronate, clodronate, tiludronate and nitrogen containing BPs such as pamidronate, alendronate, ibandronate, risedronate and zoledronate. All BPs have a high affinity for calcium and in the body, they concentrate in the skeleton at sites of active bone remodeling. Both classes of BPs become embedded in new bone during the anabolic phase of remodeling by binding to the hydroxyapatite of bone, where they remain inert. When bone containing a BP is resorbed the BPs are released in the acidic lacuna created by the osteoclast, and are taken up by these cells. The non-nitrogen containing BPs induce apoptosis in the osteoclast by incorporating into ATP and thereby reduce resorption by decreasing the number of active osteoclast cells on the bone surface. The more widely used nitrogen containing BPs inhibit farnesyl pyrophosphate synthase (FPPS), a key enzyme in the mevalonate pathway. This results in cytoskeletal changes in the osteoclast, which inhibit the activity of the osteoclast and or may induce apoptosis of these cells. Similar to the non-nitrogen containing BPs, the net result is a decrease in osteoclastic bone resorption. Because these compounds become entombed in the bone, they reside in the body long after treatment cessation and indeed, the calculated half-life of elimination of BPs from the skeleton is up to 10 years (reviewed in [3]). This is substantiated by the observation of detectable levels of pamidronate in the urine of patients 8 years after they had ceased treatment [4]. Given that resorption of bone by the osteoclast is a key component of fracture repair, concerns have been raised regarding BP associated inhibition of the repair process, both in situations where there has been past use of these compounds and it is known that BPs have been retained in the skeleton and in cases of acute treatment after fracture.

MATERIALS AND METHODS

A literature search of Medline, Google Scholar and PubMed was performed for articles addressing the subject of bisphosphonates on fracture healing and this literature search yielded 275 citations (search conducted in December, of 2014). Included among our search

findings were two recent reviews of meta-analyses of human studies and these papers were not considered as a primary reference, yielding 273 papers for consideration.[5, 6] Several of the articles identified addressed the topic of preclinical fracture healing with bisphosphonates. In addition to database queries, the reference lists of potentially relevant articles were also examined to identify additional relevant studies. Inclusion criteria for consideration of studies for this literature review included: 1) papers were written in English, 2) publication of the study findings in peer-reviewed journals and 3) in vitro and in vivo studies that evaluated the implication of Bisphosphonates on fracture healing. We used the following exclusion criteria: 1) articles using languages other than English and 2) letters, reviews, expert opinion publications or other articles that were not primary reports of findings. Articles meeting the above mentioned criteria were retrieved and all of the studies related to these were extensively reviewed.

RESULTS

The search strategies yielded a total of 273 potential articles. During the selection process, the articles were excluded by title and or by abstract, because they were clearly irrelevant to the study question. The papers meeting our inclusion criteria are described in greater detail below. These papers could be distributed into two main categories. The first category was comprised of studies which investigated the effects of BPs in animal models and the second category included the studies which examined effects of BPs use on human fracture healing.

Preclinical animal models

Several animal models have been used to examine the effects of BPs on fracture healing including mice, rats, rabbits, dogs and ovine models. Using these models, the impact of bisphosphonate administration on indirect fracture healing (healing with callus) has been extensively examined and the results have been remarkably consistent, but direct fracture healing has been less well studied. Overall, these studies of indirect healing suggest that BP administration appears to decrease the remodeling of fracture callus with a concomitant increase in fracture bridging and or retained cancellous bone structures within the callus [7, 8] but it is apparent that BPs do not interfere with the formation of the callus itself [8-15]. As a result, there is a delay in the conversion of the woven bone at the fracture to mature lamellar bone. [16]

Indirect Fracture Healing—Fu and colleagues studied fracture callus properties in ovariectomized rats using alendronate long-term and found a larger fracture callus formed in the treated animals. However, despite the observation of a delayed conversion of woven bone to lamellar bone in the intervention group, the mechanical properties of the callus were similar to control animals.[16] Manabe et al. found similar findings using ibandronate. In this study, the authors noted that extending the dosing interval could mitigate the delay of conversion of woven bone to lamellar bone in the callus.[17]

Kidd and colleagues studied the effects of either a high or low dose of risedronate on stress fracture healing in a rat ulna model. In the animals treated with the higher dose (1.0 mg/kg, twice the normal dose for osteoporosis treatment), they found a delay in healing. Specifically they noted a reduction in bone resorption and in new bone formation along the

fracture line at 6 and 10 weeks post fracture. This delay in healing was not observed in the animals treated with a low dose (0.1 mg/kg). Regardless of the dose of risedronate used, they observed no interference with callus formation.[18] Sloan and colleagues had similar findings study in which the effects of alendronate were examined.[19]

Yu and colleagues noted that early in fracture repair, there was a delay in cartilage hypertrophy and in angiogenesis and later in the repair, there a delay in remodeling of the callus, cartilage and bone in mice treated with zoledronate. This effect was more pronounced in mandible fracture healing than tibia fracture healing in their study [20]. It must be note though that this is in stark contrast to studies in rabbits, in which use of zoledronic acid was observed to *accelerate* mandible fracture healing.[21]

Bosemark et al. used a combination of zoledronate and BMP7 in an autograft healing model in rats. While they did observe an effect of just BMP7 alone, the combined therapy resulted in a substantial increase in callus volume and a four-fold increase in mechanical strength at the healed fracture site as compared to the repair observed in the controls. The impact of the combined therapy was nearly double that for the BMP7 treatment alone with regards to callus volume and ultimate force at failure at the fracture site. [22] In a follow up study, this same group examined the combination of BMP7 and zoledronate on healing in an allograph model and found a very similar result. [23] Doi and colleagues examined the impact of zoledronic acid plus BMP2 in a rat femoral fracture model and determined that healed fractures from rats treated with either zoledronic acid alone or zoledronic acid combination with BMP2 showed greater ultimate load at failure and greater stiffness than either the control treated animals or the animals treated with BMP2 alone. The authors further concluded that the combination of BMP2 and zoledronic acid enhanced fracture fusion.[24]

Another group studied low-intensity, pulsed ultrasound combined with alendronate in a rat osteotomy model, wherein the fracture was fixed with intramedullary pin. An increase in bone mineral density at the osteotomy site was observed in the ultrasound treatment alone group, the alendronate treatment alone group and in the combined treatment groups, with the greatest effect seen in the combined treatment animals. However, no mechanical testing of the healed bone was conducted in this study. [25]

Direct Fracture Healing—Direct bone healing is typically seen with rigid internal fixation such as compression plating of a transverse fracture undergoing direct osteonal healing. Using rats wherein an osteotomy was rigidly fixed with a compression plate, Savaridas and colleagues examined the impact of ibandronate given three weeks prior to fracture. They showed impairment in progression to fracture union, a reduction in mean stress at failure as assessed by 4 point bending and reduction of bone mineral density at the osteotomy site in the treated animals versus controls. Lastly, they observed the presence of cartilage-like tissue and undifferentiated mesenchymal tissue at the osteotomy site. [26]

Human studies of acute fracture healing after short term and long term use of BPs

Bisphosphonates are the most commonly used therapy in humans for osteoporosis treatment. Like what was found using pre-clinical models, most studies report that fracture callus formation is larger but that healing is not impaired in patients treated with bisphosphonates

compared with untreated patients.(reviewed in [27, 28]) Indeed, a large meta-analysis of 8 randomized controlled trials using BPs with fracture healing as an endpoint concluded there was no delay in callus formation or healing.[5]

In general, the finding of no impact of BPs on fracture healing was observed in studies focused on specific types or sites of fractures, but this was not a universal observation. For example, the use of zoledronic acid give to the patient after fracture, irrespective of the timing post fracture, has not been shown to affect fracture healing in two separate studies of hip fracture patients.[6, 29]. In the upper extremity, bisphosphonates have been studied for many different types of fractures and likewise, most authors report no significant delay in union in these fractures with BP use immediately after the fracture, but an increase in risk of fracture non-union was reported. Conversely, fracture healing in patients already on BP at the time of fracture was reported to be slightly delayed, but there was no difference in non-union incidence.[30] Similarly, Rozental and colleagues report that BP use prior to distal radius fracture resulted in <1 week of delay in healing, but in a separate study, the early administration of BPs after distal radius fracture did not result in a delay in healing.[31, 32] One key instance in which many authors report delayed healing to occur is with long-term use of bisphosphonates and development of atypical femoral fractures.[33, 34] Unfortunately, a delay in healing was reported to occur in 26% of cases of these rare fractures.[35]

DISCUSSION

Considerable study of the effects of BPs on fracture healing has been done using animal models and essentially all species studied exhibit formation of larger bony callus and delayed remodeling of woven bone into lamellar bone with use of this class of compounds. Despite this deviation from the normal pattern of healing, this larger callus size seen in BP treated animals was usually reported to be mechanically equivalent to but not superior to that found in the control animals. The increases in biomechanical strength may be due to the retention of trabecular elements in the callus and or increased fracture bridging. It should be noted that the timing of BP dosing relative to the time of fracture does appear to influence this delay in healing.

Comparatively speaking, there are fewer human studies that have been performed with BPs used around the time of fracture healing. In all of the studies reported to date, there has been no significant delay noted in upper extremity or lower extremity fractures when BP therapy was initiated right after fracture. Conversely, in patients already on long-term BP therapy who sustain an atypical femoral fracture (a clinically rare event), a delay in bony union was observed an estimated 26% of the time[35]. At this time, there is insufficient data regarding any delay in healing in patients using long-term BP who suffer more typical fractures and as such this clinical situation is not fully understood. Similarly, there is a paucity of information about the benefits of "drug holidays" during long-term BP use upon suffering of fracture.

CONCLUSION

Animal models of BP use show no delay in periosteal healing but a significant effect on fracture remodeling was consistently observed. BPs do not appear to delay human fracture healing when the use of these compounds is initiated following the acute fracture, regardless of the timing of the initiation of treatment during the healing period. Conversely, there is some evidence to suggest that BP therapy should be stopped in patients that have been already treated long-term with BPs and then suffer an atypical fracture. Cessation of BP use (drug holiday) at the time of fracture may also be prudent after long-term treatment with this class of drugs, however this remains a topic of investigation.

REFERENCES

1. MARSELL R, EINHORN TA. THE BIOLOGY OF FRACTURE HEALING. INJURY. 2011; 42:551–5. [PubMed: 21489527]

2. HADJIARGYROU M, O'KEEFE RJ. THE CONVERGENCE OF FRACTURE REPAIR AND STEM CELLS: INTERPLAY OF GENES, AGING, ENVIRONMENTAL FACTORS AND DISEASE. J BONE MINER RES. 2014; 29:2307–22. [PubMed: 25264148]

3. PAPAPOULOS, SE. BISPHOSPHONATES FOR POSTMENOPAUSAL OSTEOPOROSIS.. In: ROSEN, CJ., editor. PRIMER ON THE METABOLIC BONE DISEASES AND DISORDERS OF MINERAL METABOLISM. 8TH ED. WILEY-BLACKWELL; 2013. p. 412-9.

4. PAPAPOULOS SE, CREMERS SC. PROLONGED BISPHOSPHONATE RELEASE AFTER TREATMENT IN CHILDREN. N ENGL J MED. 2007; 356:1075–6. [PubMed: 17347467]

5. XUE D, LI F, CHEN G, YAN S, PAN Z. DO BISPHOSPHONATES AFFECT BONE HEALING? A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS. J ORTHOP SURG RES. 2014; 9:45. [PubMed: 24902588]

6. LI YT, CAI HF, ZHANG ZL. TIMING OF THE INITIATION OF BISPHOSPHONATES AFTER SURGERY FOR FRACTURE HEALING: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS. OSTEOPOROS INT. 2014

7. AMANAT N, MCDONALD M, GODFREY C, BILSTON L, LITTLE D. OPTIMAL TIMING OF A SINGLE DOSE OF ZOLEDRONIC ACID TO INCREASE STRENGTH IN RAT FRACTURE REPAIR. J BONE MINER RES. 2007; 22:867–76. [PubMed: 17371160]

8. GOODSHIP AE, WALKER PC, MCNALLY D, CHAMBERS T, GREEN JR. USE OF A BISPHOSPHONATE (PAMIDRONATE) TO MODULATE FRACTURE REPAIR IN OVINE BONE. ANN ONCOL. 1994; 5(SUPPL 7):S53–5. [PubMed: 7873463]

9. MATOS MA, TANNURI U, GUARNIERO R. THE EFFECT OF ZOLEDRONATE DURING BONE HEALING. J ORTHOP TRAUMATOL. 2010; 11:7–12. [PubMed: 20169393]

10. GERSTENFELD LC, SACKS DJ, PELIS M, MASON ZD, GRAVES DT, BARRERO M, et al. COMPARISON OF EFFECTS OF THE BISPHOSPHONATE ALENDRONATE VERSUS THE RANKL INHIBITOR DENOSUMAB ON MURINE FRACTURE HEALING. J BONE MINER RES. 2009; 24:196–208. [PubMed: 19016594]

11. MATOS MA, ARAUJO FP, PAIXAO FB. THE EFFECT OF ZOLEDRONATE ON BONE REMODELING DURING THE HEALING PROCESS. ACTA CIR BRAS. 2007; 22:115–9. [PubMed: 17375217]

12. AMANAT N, BROWN R, BILSTON LE, LITTLE DG. A SINGLE SYSTEMIC DOSE OF PAMIDRONATE IMPROVES BONE MINERAL CONTENT AND ACCELERATES RESTORATION OF STRENGTH IN A RAT MODEL OF FRACTURE REPAIR. JOURNAL OF ORTHOPAEDIC RESEARCH : OFFICIAL PUBLICATION OF THE ORTHOPAEDIC RESEARCH SOCIETY. 2005; 23:1029–34. [PubMed: 16140188]

13. BAUSS F, SCHENK RK, HORT S, MULLER-BECKMANN B, SPONER G. NEW MODEL FOR SIMULATION OF FRACTURE REPAIR IN FULL-GROWN BEAGLE DOGS: MODEL CHARACTERIZATION AND RESULTS FROM A LONG-TERM STUDY WITH

IBANDRONATE. J PHARMACOL TOXICOL METHODS. 2004; 50:25–34. [PubMed: 15233964]

14. LI J, MORI S, KAJI Y, MASHIBA T, KAWANISHI J, NORIMATSU H. EFFECT OF BISPHOSPHONATE (INCADRONATE) ON FRACTURE HEALING OF LONG BONES IN RATS. J BONE MINER RES. 1999; 14:969–79. [PubMed: 10352106]

15. PETER CP, COOK WO, NUNAMAKER DM, PROVOST MT, SEEDOR JG, RODAN GA. EFFECT OF ALENDRONATE ON FRACTURE HEALING AND BONE REMODELING IN DOGS. JOURNAL OF ORTHOPAEDIC RESEARCH : OFFICIAL PUBLICATION OF THE ORTHOPAEDIC RESEARCH SOCIETY. 1996; 14:74–9. [PubMed: 8618170]

16. FU LJ, TANG TT, HAO YQ, DAI KR. LONG-TERM EFFECTS OF ALENDRONATE ON FRACTURE HEALING AND BONE REMODELING OF FEMORAL SHAFT IN OVARIECTOMIZED RATS. ACTA PHARMACOL SIN. 2013; 34:387–92. [PubMed: 23459092]

17. MANABE T, MORI S, MASHIBA T, KAJI Y, IWATA K, KOMATSUBARA S, et al. EFFECT OF DOSING INTERVAL DURATION OF INTERMITTENT IBANDRONATE TREATMENT ON THE HEALING PROCESS OF FEMORAL OSTEOTOMY IN A RAT FRACTURE MODEL. CALCIF TISSUE INT. 2012; 90:193–201. [PubMed: 22249523]

18. KIDD LJ, COWLING NR, WU AC, KELLY WL, FORWOOD MR. BISPHOSPHONATE TREATMENT DELAYS STRESS FRACTURE REMODELING IN THE RAT ULNA. JOURNAL OF ORTHOPAEDIC RESEARCH : OFFICIAL PUBLICATION OF THE ORTHOPAEDIC RESEARCH SOCIETY. 2011; 29:1827–33. [PubMed: 21598308]

19. SLOAN AV, MARTIN JR, LI S, LI J. PARATHYROID HORMONE AND BISPHOSPHONATE HAVE OPPOSITE EFFECTS ON STRESS FRACTURE REPAIR. BONE. 2010; 47:235–40. [PubMed: 20580684]

20. YU YY, LIEU S, HU D, MICLAU T, COLNOT C. SITE SPECIFIC EFFECTS OF ZOLEDRONIC ACID DURING TIBIAL AND MANDIBULAR FRACTURE REPAIR. PLOS ONE. 2012; 7:E31771. [PubMed: 22359627]

21. TATLI U, USTUN Y, KURKCU M, ERDOGAN O, GURBUZ CC, OZGUR H, et al. EFFECTS OF ZOLEDRONIC ACID ON HEALING OF MANDIBULAR FRACTURES: AN EXPERIMENTAL STUDY IN RABBITS. J ORAL MAXILLOFAC SURG. 2011; 69:1726–35. [PubMed: 21256644]

22. BOSEMARK P, ISAKSSON H, MCDONALD MM, LITTLE DG, TAGIL M. AUGMENTATION OF AUTOLOGOUS BONE GRAFT BY A COMBINATION OF BONE MORPHOGENIC PROTEIN AND BISPHOSPHONATE INCREASED BOTH CALLUS VOLUME AND STRENGTH. ACTA ORTHOPAEDICA. 2013; 84:106–11. [PubMed: 23409846]

23. MATHAVAN N, BOSEMARK P, ISAKSSON H, TAGIL M. INVESTIGATING THE SYNERGISTIC EFFICACY OF BMP-7 AND ZOLEDRONATE ON BONE ALLOGRAFTS USING AN OPEN RAT OSTEOTOMY MODEL. BONE. 2013; 56:440–8. [PubMed: 23845325]

24. DOI Y, MIYAZAKI M, YOSHIIWA T, HARA K, KATAOKA M, TSUMURA H. MANIPULATION OF THE ANABOLIC AND CATABOLIC RESPONSES WITH BMP-2 AND ZOLEDRONIC ACID IN A RAT FEMORAL FRACTURE MODEL. BONE. 2011; 49:777–82. [PubMed: 21777711]

25. AONUMA H, MIYAKOSHI N, KASUKAWA Y, KAMO K, SASAKI H, TSUCHIE H, et al. COMBINED TREATMENT OF ALENDRONATE AND LOW-INTENSITY PULSED ULTRASOUND (LIPUS) INCREASES BONE MINERAL DENSITY AT THE CANCELLOUS BONE OSTEOTOMY SITE IN AGED RATS: A PRELIMINARY STUDY. JNMA J NEPAL MED ASSOC. 2011; 51:171–5. [PubMed: 22922896]

26. SAVARIDAS T, WALLACE RJ, SALTER DM, SIMPSON AH. DO BISPHOSPHONATES INHIBIT DIRECT FRACTURE HEALING?: A LABORATORY INVESTIGATION USING AN ANIMAL MODEL. BONE JOINT J. 2013; 95-B:1263–8. [PubMed: 23997143]

27. LARSSON S, FAZZALARI NL. ANTI-OSTEOPOROSIS THERAPY AND FRACTURE HEALING. ARCH ORTHOP TRAUMA SURG. 2014; 134:291–7. [PubMed: 22684739]

28. BUKATA SV. SYSTEMIC ADMINISTRATION OF PHARMACOLOGICAL AGENTS AND BONE REPAIR: WHAT CAN WE EXPECT. INJURY. 2011; 42:605–8. [PubMed: 21507402]

29. COLON-EMERIC C, NORDSLETTEN L, OLSON S, MAJOR N, BOONEN S, HAENTJENS P, et al. ASSOCIATION BETWEEN TIMING OF ZOLEDRONIC ACID INFUSION AND HIP FRACTURE HEALING. OSTEOPOROS INT. 2011; 22:2329–36. [PubMed: 21153021]

30. NG AJ, YUE B, JOSEPH S, RICHARDSON M. DELAYED/NON-UNION OF UPPER LIMB FRACTURES WITH BISPHOSPHONATES: SYSTEMATIC REVIEW AND RECOMMENDATIONS. ANZ J SURG. 2014; 84:218–24. [PubMed: 24529100]

31. UCHIYAMA S, ITSUBO T, NAKAMURA K, FUJINAGA Y, SATO N, IMAEDA T, et al. EFFECT OF EARLY ADMINISTRATION OF ALENDRONATE AFTER SURGERY FOR DISTAL RADIAL FRAGILITY FRACTURE ON RADIOLOGICAL FRACTURE HEALING TIME. BONE JOINT J. 2013; 95-B:1544–50. [PubMed: 24151277]

32. GONG HS, SONG CH, LEE YH, RHEE SH, LEE HJ, BAEK GH. EARLY INITIATION OF BISPHOSPHONATE DOES NOT AFFECT HEALING AND OUTCOMES OF VOLAR PLATE FIXATION OF OSTEOPOROTIC DISTAL RADIAL FRACTURES. THE JOURNAL OF BONE AND JOINT SURGERY AMERICAN VOLUME. 2012; 94:1729–36. [PubMed: 22992762]

33. EGOL KA, PARK JH, ROSENBERG ZS, PECK V, TEJWANI NC. HEALING DELAYED BUT GENERALLY RELIABLE AFTER BISPHOSPHONATE-ASSOCIATED COMPLETE FEMUR FRACTURES TREATED WITH IM NAILS. CLINICAL ORTHOPAEDICS AND RELATED RESEARCH. 2014; 472:2728–34. [PubMed: 23604648]

34. MIYAKOSHI N, AIZAWA T, SASAKI S, ANDO S, MAEKAWA S, AONUMA H, et al. HEALING OF BISPHOSPHONATE-ASSOCIATED ATYPICAL FEMORAL FRACTURES IN PATIENTS WITH OSTEOPOROSIS: A COMPARISON BETWEEN TREATMENT WITH AND WITHOUT TERIPARATIDE. J BONE MINER METAB. 2014

35. EDWARDS BJ, BUNTA AD, LANE J, ODVINA C, RAO DS, RAISCH DW, et al. BISPHOSPHONATES AND NONHEALING FEMORAL FRACTURES: ANALYSIS OF THE FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) AND INTERNATIONAL SAFETY EFFORTS: A SYSTEMATIC REVIEW FROM THE RESEARCH ON ADVERSE DRUG EVENTS AND REPORTS (RADAR) PROJECT. THE JOURNAL OF BONE AND JOINT SURGERY AMERICAN VOLUME. 2013; 95:297–307. [PubMed: 23426763]