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Bisphosphonates for Postmenopausal Osteoporosis

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Bisphosphonates (BPs) are synthetic compounds that have high affinity for calcium crystals, concentrate selectively in the skeleton, and decrease bone resorption. The first BP was synthesized in the 19th century but their relevance to medicine was recognized in the 1960s, and they were first given to patients with osteoporosis in the early 1970s. Currently, alendronate, ibandronate, risedronate, and zoledronate are approved for the treatment of osteoporosis worldwide while other BPs are also available in some countries.

PHARMACOLOGY

BPs are synthetic analogs of inorganic pyrophosphate in which the oxygen atom that connects the two phosphates is replaced by a carbon (Fig. 49.1). This substitution renders BPs resistant to biological degradation and suitable for clinical use. BPs have two additional side chains (R1 and R2) that allow the synthesis of a large number of analogs with different pharmacological properties (Fig. 49.1). A hydroxyl substitution at R1 enhances the affinity of BPs for calcium crystals, while the presence of a nitrogen atom in R2 enhances their potency and determines their mechanism of action. The whole molecule is responsible for the action of BPs on bone resorption and probably also for their affinity for bone mineral [1, 2].

The intestinal absorption of BPs is poor (less than 1%) and decreases further in the presence of food, calcium, or other minerals that bind them. Oral BPs should be given in the fasting state 30 to 60 minutes before meals, with water. BPs are cleared rapidly from the circulation; about 50% of the administered dose concentrates in the skeleton, primarily at active remodeling sites, while the rest is excreted unmetabolized in urine. Skeletal uptake depends on the rate of bone turnover, renal function, as well as on the structure of BPs [3]. The capacity of the skeleton to retain BP is large, and saturation of binding sites with the doses used in the treatment of osteoporosis is unlikely even if these are given for a very long time. At the bone surface, BPs inhibit bone resorption and are subsequently embedded in bone where they remain for long and are pharmacologically inactive. The elimination of BPs from the body is multiexponential; the calculated terminal half-life of elimination from the skeleton can be as long as 10 years, and pamidronate has been detected in urines of patients for up to 8 years after discontinuation of treatment. This slow release of the BP from the skeleton is probably responsible for the slow speed of reversal of the effect of BPs on bone following cessation of treatment, which is different from that of all other antiosteoporotic treatments. The rate of reversal of the effect may be different among BPs depending on their pharmacological properties, particularly their affinity for bone mineral, but no head-to-head studies have addressed this issue in humans.

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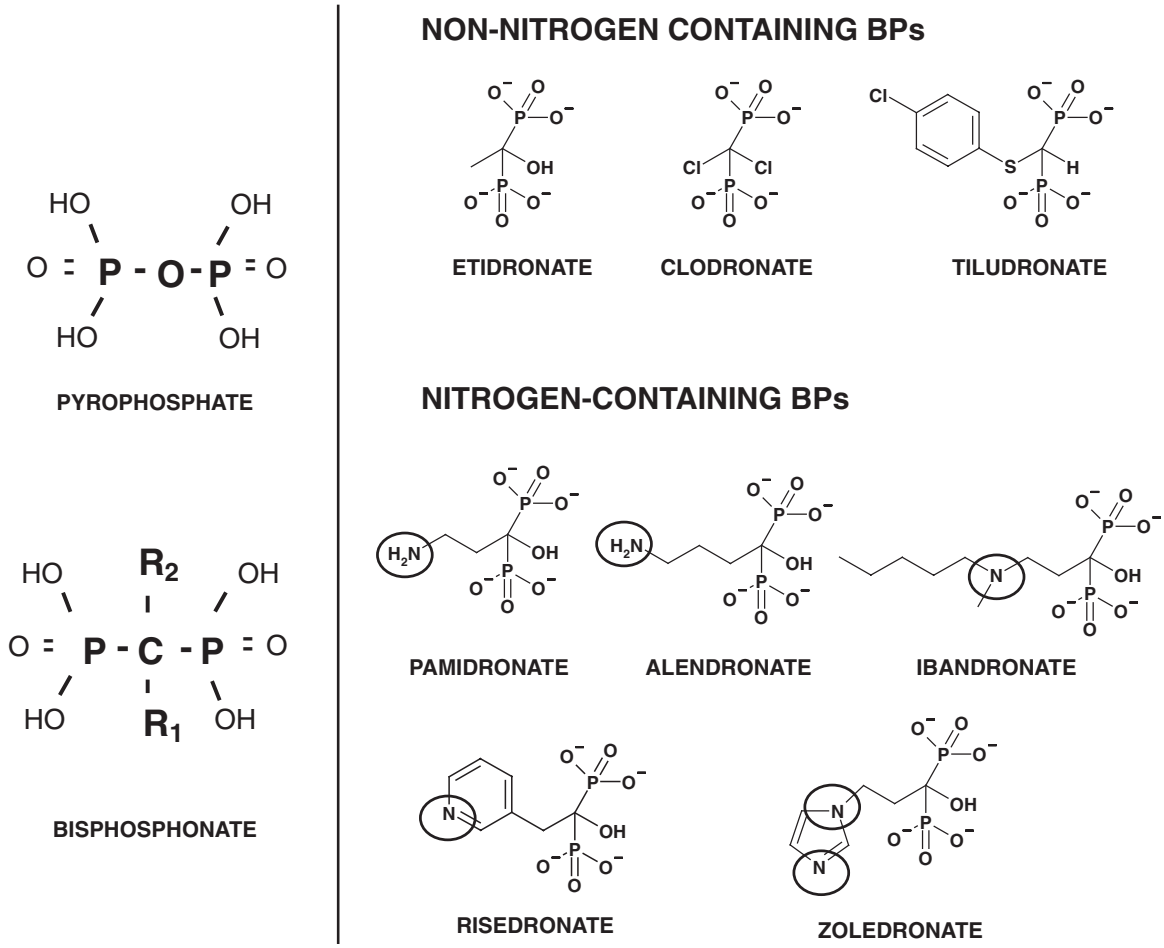

Fig. 49.1. *Left panel*: Structure of pyrophosphate and geminal bisphosphonates. *Right panel*: Structures of clinically used bisphosphonates (acid forms are depicted).

The decrease of bone resorption by BPs is followed by a slower decrease in the rate of bone formation, due to the coupling of the two processes, so that a new steady state at a lower rate of bone turnover is reached 3 to 6 months after the start of treatment. This level of bone turnover remains constant during the whole period of treatment, demonstrating that the accumulation of BP in the skeleton is not associated with a cumulative effect on bone turnover. In addition to decreasing the rate of bone turnover to premenopausal levels, BPs maintain or may improve trabecular and cortical architecture, improve the hypomineralization of osteoporotic bone, increase areal mineral density and may reduce the rate of osteocyte apoptosis. The relevant clinical outcome of these actions is the decrease of the risk of fractures (Fig. 49.2).

At the cellular level BPs inhibit the activity of osteoclasts [1, 4]. BPs bound to bone hydroxyapatite are released in the acidic environment of the resorption lacunae under the osteoclasts and are taken up by them. BPs without a nitrogen atom in their molecule (Fig. 49.1) incorporate into ATP and generate metabolites that induce osteoclast apoptosis. Nitrogen-containing BPs (N-BPs) induce changes in the cytoskeleton of osteoclasts leading to their inactivation and potentially apoptosis. This action is mainly the result of inhibition of farnesyl pyrophosphate synthase (FPPS), an enzyme of the mevalonate biosynthetic pathway. FPPS is responsible for the formation of isoprenoid metabolites required for the prenylation of small GTPases that are important for cytoskeletal integrity and function of osteoclasts. There is a close relation between the degree of inhibition of FPPS and the antiresorptive potencies of N-BPs. In addition, the inhibition of FPPS by N-BPs leads to accumulation of IPP, a metabolite immediately upstream of FPPS, which reacts with adenosine monophosphate (AMP) leading to the production of a new metabolite which induces osteoclast apoptosis.

ANTIFRACTURE EFFICACY

All BPs given daily in adequate doses reduce significantly the risk of vertebral fractures by 35 to 65 % (Fig. 49.3)

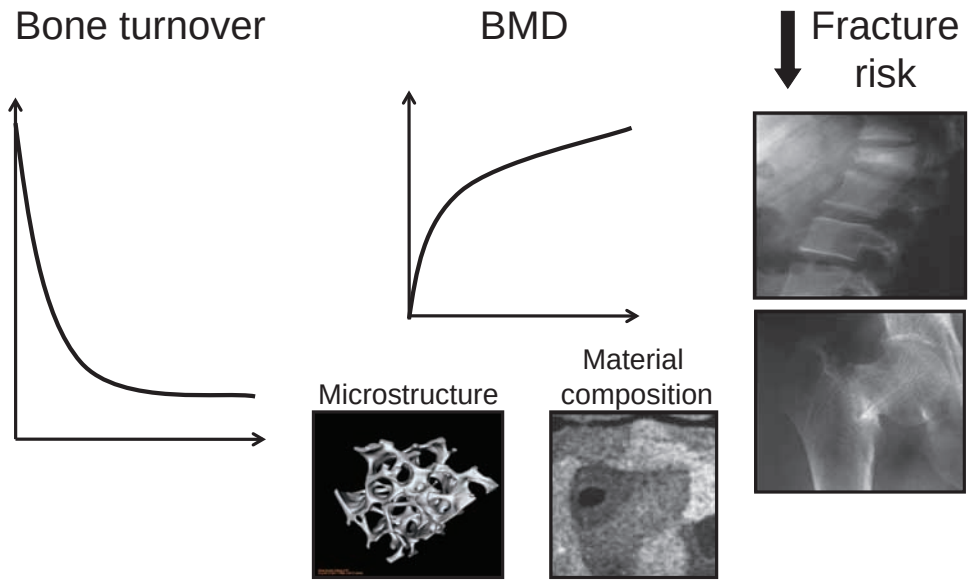

Fig. 49.2. Schematic presentation of effects of bisphosphonates on bone metabolism and strength in osteoporosis.

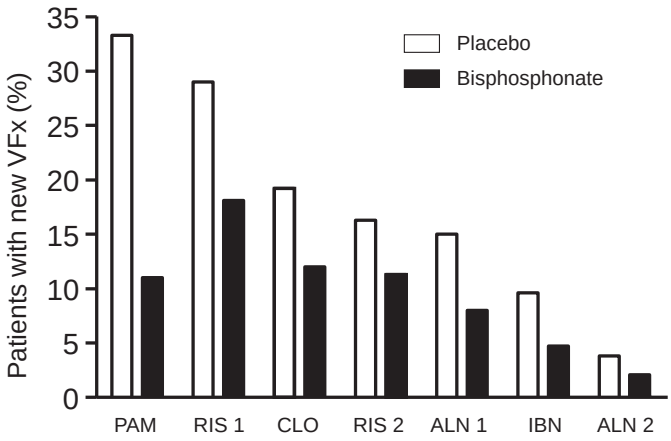

Fig. 49.3. Incidence of fractures in patients with osteoporosis treated with daily oral placebo (open bars) or bisphosphonate (closed bars) after 3 years. PAM = pamidronate (Ref. 5); RIS 1 = risedronate (VERT multinational study; Ref, 9); CLO = clodronate (Ref. 11); RIS 2 = risedronate (VERT North America study; Ref. 8); ALN 1 = alendronate (FIT 1 study; Ref. 6); IBN = ibandronate (BONE study; Ref, 10); ALN 2 = alendronate (FIT 2 study; Ref. 7).

[5–11]. Also illustrated in Fig. 49.3 are the large differences in the incidence of fractures among placebo-treated patients. Results, therefore, of different clinical trials should not be used to compare efficacy of individual BPs. For that, head-to-head studies are needed, but these are not available. The overall efficacy and consistency of daily BPs in reducing the risk of vertebral fractures has been demonstrated by meta-analyses of randomized controlled trials (RCTs) for alendronate and risedronate [12–14]. In studies in which radiographs were taken annually (e.g., the Vertebral Efficacy with Risedronate Therapy (VERT) study with risedronate), the effect of the BP in reducing the risk of vertebral fractures was already evident after 1 year, demonstrating rapid protection of skeletal integrity. This was also shown for moderate and severe vertebral fractures with ibandronate [15] and for clinical vertebral fractures with alendronate [16]. A *post hoc* analysis of risedronate trials reported a significant reduction in clinical vertebral fractures as early as 6 months after the start of treatment [17].

The efficacy of daily oral BPs in reducing the risk of nonvertebral fractures was explored in a number of RCTs. It should be noted that definitions and adjudication procedures of nonvertebral fractures were different among clinical trials. A meta-analysis of the Cochrane Collaboration reported an overall reduction of the risk of nonvertebral fractures in women with osteoporosis of 23% (RR 0.77; 95% CI 0.74–0.94) with alendronate and 20% (RR 0.80; 95% CI 0.72–0.90) with risedronate [13, 14]. The corresponding risk reductions for hip fractures were 53% (RR 0.47; 95% CI 0.26–0.85) with alendronate and 26% (RR 0.74; 95% CI 0.59–0.94%) with risedronate. These estimates are in agreement with earlier published meta-analyses [18, 19]. With daily ibandronate, a reduction (69%) in the risk of nonvertebral fractures was reported in a population at high risk [femoral neck bone mineral density (BMD) below –3.0] by *post hoc* analysis [10]. As with vertebral fractures, the effect of BPs on nonvertebral fractures occurs early after the start of treatment.

Daily administration of BPs, though highly efficacious, is inconvenient and may also be associated with gastrointestinal adverse effects. These reduce adherence to treatment and can diminish the therapeutic response [20,21]. To overcome both these problems, once-weekly

formulations, the sum of seven daily doses, have been developed for alendronate and risedronate, and were shown to significantly improve patient adherence to treatment while sustaining the same pharmacodynamic response as the daily treatment [22, 23]. A once-weekly slow-release formulation of risedronate that can be administered after breakfast is also available. Daily and weekly BPs are pharmacologically equivalent and should be considered as continuous administration while the term "intermittent" or "cyclical administration" should be reserved for treatments with drug-free intervals longer than 2 weeks [3].

Intermittent administration of BPs

Results of early attempts to give bisphosphonates intermittently to patients with osteoporosis were equivocal but a meta-analysis of studies with cyclical etidronate showed a significant reduction in the risk of vertebral, but not nonvertebral, fractures [24]. The efficacy of intermittent administration of N-BPs was explored in studies with ibandronate, which indicated that dose and dosing intervals are important determinants of the response to intermittent BP therapy, which in turn depends on the safety and tolerability of the administered dose [25]. An oral ibandronate preparation given once monthly and an intravenous preparation given once every 3 months, providing higher cumulative doses than the daily regimen, were developed and were shown to significantly increase BMD and reduce the risk of nonvertebral fractures by 38% compared to the oral daily dose [26, 27]. A once-monthly oral preparation of risedronate is also available.

The efficacy of intermittent administration of zoledronate, the most potent N-BP, in reducing the risk of osteoporotic fractures was examined in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) trial, in which postmenopausal women with osteoporosis were randomized to receive 15-minute infusions of zoledronate 5 mg or placebo once-yearly [28]. Compared to placebo, zoledronate reduced the incidence of vertebral fractures by 70%, hip fractures by 41%, and nonvertebral fractures by 25% after 3 years. The effect of zoledronate on vertebral fractures was already significant at 1 year. In a second controlled study [29], zoledronate infusions given within 90 days after surgical repair of a hip fracture decreased significantly the rate of new clinical fractures by 35% and improved patient survival (28% reduction in all-cause mortality). Epidemiological studies reported also survival benefits in patients treated with oral BPs [30–32].

LONG-TERM EFFECTS ON BONE FRAGILITY

Skeletal fragility on long-term BP therapy has been examined in extensions of four clinical trials for 6 to 10 years [33–36]. None of these extension studies were specifically designed to assess antifracture efficacy; rather, safety and efficacy of surrogate end points, as well as the consistency of the effect of BPs over longer periods, were evaluated. In all four studies, the incidence of nonvertebral fractures was constant with time. In the extension of the FIT (Fracture Intervention Trial) (FLEX), patients who received on average alendronate for 5 years were randomized to placebo, alendronate 5 mg/day or alendronate 10 mg/day, and were followed for another 5 years [35]. Continuation of alendronate treatment led to further increases in BMD of the spine and stabilization of that of the hip, whereas there was a slow progressive decrease of the total hip BMD in patients who received a placebo during the extension. At the end of the 10-year observation period, the incidence of nonvertebral and hip fractures in the ALN/PBO group was similar to that of the ALN/ALN groups. In addition, the incidence of clinical vertebral fractures was lower in the ALN/ALN groups compared to the ALN/PBO group (2% vs 5 %). In a *post hoc* analysis, women who entered the extension with a femoral neck BMD T-score below –2.5 BMD and no vertebral fractures and continued treatment with alendronate showed a significant reduction in the risk of nonvertebral fractures during the 5-year extension. These results suggest that alendronate treatment should be continued in patients at high risk whereas discontinuation of treatment after 5 years may be considered in patients with lower fracture risk. Similar BMD and fracture data were recently reported in the extension of the HORIZON trial in which patients treated with zoledronate for 3 years were randomized to 3 additional years of zoledronate or placebo [36].

SPECIAL ISSUES RELATED TO TREATMENT OF OSTEOPOROSIS WITH BISPHOSPHONATES

Excessive suppression of bone remodeling

There have been concerns that the long-term decrease of bone remodeling by BPs may compromise bone integrity leading to increased bone fragility. Numerous studies in different animal models with N-BPs given at a wide range of doses and time intervals have consistently shown preservation or improvement of bone strength. In only one study with high doses of clodronate given to healthy dogs an increase in fracture incidence has been reported. Earlier reports of potential compromise of the biomechanical competence of bone due to increases in microdamage accumulation in bone biopsies of healthy dogs treated with high BP doses were not substantiated by later animal and human studies [37, 38]. In human controlled studies of osteoporosis, the incidence of nonvertebral fractures was not increased with long-term therapy. and bone turnover markers increased after cessation of treatment, which indicated metabolically active bone. In

addition, an analysis of the FIT data showed that higher decreases of bone turnover were associated with larger decreases in the incidence of nonvertebral and hip fractures [39], a finding supported by the above-mentioned analysis of the ibandronate studies. Moreover, in studies of patients treated with BPs followed by treatment with teriparatide, early significant increases in bone markers have been reported, indicating that BP-treated bone can readily respond to stimuli [40]. This conclusion is further supported by a study of zoledronate treatment of patients previously treated with alendronate, which showed that alendronate-treated bone reacted normally to an acute BP load, as provided by zoledronate, indicating that metabolic activity was preserved [41].

Atypical fractures of the femur

In recent years there has been growing concern about the potential relationship between unusual low-energy subtrochanteric/diaphyseal femoral fractures, termed atypical, and long-term use of BPs. Atypical fractures of the femur are often preceded by prodromal pain, can be bilateral and healing may be delayed (Fig. 49.4). Criteria for the identification and diagnosis of atypical fractures of the femur have been proposed by a Task Force of the ASBMR [42]. These fractures are rare, about 1% of all femoral fractures, and occur more frequently in patients treated with BPs than in untreated patients [43, 44]. However, a causal association between BPs and atypical fractures has not been established but appears that the risk rises with increasing duration of exposure.

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) is defined as exposed bone in the mandible, maxilla, or both that persists for at least 8 weeks in the absence of previous irradiation or metastases in the jaw. It has been reported mainly in patients with malignant diseases receiving high intravenous doses of BPs. The background incidence in the population and its pathogenesis are poorly defined, and a causal relation with BPs has not been established. In patients with osteoporosis treated with BPs, ONJ is rare; an incidence between 1:10,000 and <1:100,000 patient-years has been estimated, and appears to increase with duration of treatment [45–47]. In the two clinical trials of yearly infusions of zoledronate up to 3 years, two adjudicated cases of ONJ were reported among 9,892 patients with osteoporosis, one in the placebo-treated group and one in the zoledronate-treated group after 3 years [28, 29].

Adverse effects

BPs are relatively safe compounds, and their benefits outweigh their potential risks [48]. Specific adverse effects related to the use of BPs in osteoporosis include gastrointestinal toxicity associated with the oral, particularly daily, use of N-BPs and symptoms related to an acute phase reaction, mainly after first exposure to intravenous N-BPs. Gastrointestinal toxicity appears to be higher with generic preparations of oral BPs, of which many are currently available, resulting in significantly poorer adherence and effectiveness [49]. Case reports have suggested a relationship between oral N-BP treat-

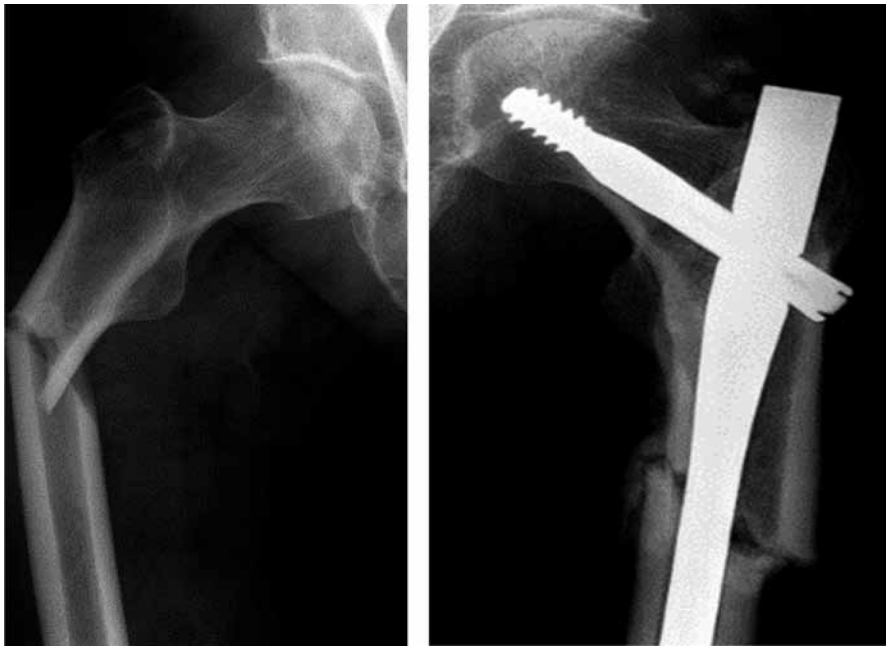

Fig. 49.4. Bilateral atypical fractures of the femur of a patient with rheumatoid arthritis on long-term treatment with alendronate and prednisone. Adapted from Somford MP, Draijer FW, Thomassen BJ, Chavassieux PM, Boivin G, Papapoulos SE. 2009. Bilateral fractures of the femur diaphysis in a patient with rheumatoid arthritis on long-term treatment with alendronate: clues to the mechanism of increased bone fragility. *J Bone Miner Res* 24: 1736–40.

ment and esophageal cancer. This was not confirmed in analyses of large databases, but a reduction in the incidence of gastric and colon cancer was recently reported in alendronate users [31, 50]. The kidney is the principal route of BP elimination, and BP use is contraindicated in patients with severely impaired renal function. Renal toxicity of intravenous BP is not a concern, provided that the indications for treatment and instructions for administration are closely followed. A significant increase in the incidence of atrial fibrillation, reported as a serious adverse event, was observed in one [28], but not in another, study [29] of patients receiving zoledronate compared to those receiving a placebo. A biological explanation for this effect is not apparent and further analyses of clinical trials with alendronate, ibandronate, and risedronate did not confirm such association.

CONCLUSIONS

BPs, because of their efficacy, safety, and ease of administration, are generally accepted as first-line therapy for osteoporosis. Selection of a BP for the treatment of an individual patient should be based on review of efficacy data, risk profile of the BP, and values and preferences of the patient. Despite progress in our understanding of the anti-fracture action of BPs and their long-term effects on bone, there are still questions that remain to be addressed. These include potential, clinically relevant, differences among BPs, optimal selection of patients for treatment and duration of use and their use in combination with bone-forming agents.

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REFERENCES

1. Russell RGG, Watts NB, Ebetino FH, Rogers MJ. 2008. Mechanisms of action of bisphosphonates: Similarities and differences and their potential influence on clinical efficacy. *Osteoporos Int* 19(6): 733–759.
2. Papapoulos SE. 2006. Bisphosphonate actions: Physical chemistry revisited. *Bone* 38: 613–616.
3. Cremers SC, Pillai G, Papapoulos SE. 2005. Pharmacokinetics/pharmacodynamics of bisphosphonates: Use for optimisation of intermittent therapy for osteoporosis. *Clin Pharmacokinet* 44: 551–570.
4. Rogers MJ, Crockett JC, Coxon FP, Monkkonen J. 2011. Biochemical and molecular mechanisms of action of bisphosphonates. *Bone* 49: 34–41.
5. Brumsen C, Papapoulos SE, Lips P, Geelhoed-Duijvestijn PHLM, Hamdy NAT, Landman JO, McCloskey EV, Netelenbos JC, Pauwels EKJ, Roos JC, Valentijn RM, Zwinderman AH. 2002. Daily oral pamidronate in women and men with osteoporosis: A 3-year randomized placebo-controlled clinical trial with a 2-year open extension. *J Bone Miner Res* 17: 1057–1064.
6. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE. 1996. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet* 348: 1535–1541.
7. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Vogt T, Wallace R, Yates AJ, LaCroix AZ 1998. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: Results from the Fracture Intervention Trial. *JAMA* 280: 2077–2082.
8. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, Chesnut CH 3rd, Brown J, Eriksen EF, Hoseyni MS, Axelrod DW, Miller PD. 1999. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: A randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA* 282: 1344–1352.
9. Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, Lund B, Ethgen D, Pack S, Roumagnac I, Eastell R. 2000. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *Osteoporos Int* 11: 83–91.
10. Chesnut CH, Ettinger MP, Miller PD, Baylink DJ, Emkey R, Harris ST, Wasnich RD, Watts NB, Schimmer RC, Recker RR. 2004. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res* 19: 1241–1249.
11. McCloskey E, Selby P, Davies M, Robinson J, Francis RM, Adams J, Kayan K, Beneton M, Jalava T, Pylkkänen L, Kenraali J, Aropuu S, Kanis JA. 2004. Clodronate reduces vertebral fracture risk in women with postmenopausal or secondary osteoporosis: Results of a double-blind, placebo-controlled 3-year study. *J Bone Miner Res* 19: 728–736.
12. Cranney A, Guyatt G, Griffith L, Wells G, Tugwell P, Rosen C; Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group. 2002. Meta-analyses of therapies for postmenopausal osteoporosis. IX: Summary of meta-analyses of therapies for postmenopausal osteoporosis. *Endocr Rev* 23: 570–578.
13. Wells G, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P. 2008. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev* 23 (1): CD004523.

14. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P. 2008. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev* 23(1): CD001155.
15. Felsenberg D, Miller P, Armbrecht G, Wilson K, Schimmer RC, Papapoulos SE. 2005. Oral ibandronate significantly reduces the risk of vertebral fractures of greater severity after 1, 2, and 3 years in postmenopausal women with osteoporosis. *Bone* 37: 651–654.
16. Black DM, Thompson DE, Bauer DC, Ensrud K, Musliner T, Hochberg MC, Nevitt MC, Suryawanshi S, Cummings SR; Fracture Intervention Trial. 2000. Fracture risk reduction with alendronate in women with osteoporosis: The Fracture Intervention Trial. FIT Research Group. *J Clin Endocrinol Metab* 85: 4118–4124.
17. Roux C, Seeman E, Eastell R, Adachi J, Jackson RD, Felsenberg D, Songcharoen S, Rizzoli R, Di Munno O, Horlait S, Valent D, Watts NB. 2004. Efficacy of risedronate on clinical vertebral fractures within six months. *Curr Med Res Opin* 20: 433–439.
18. Papapoulos SE, Quandt SA, Liberman UA, Hochberg MC, Thompson DE. 2005. Meta-analysis of the efficacy of alendronate for the prevention of hip fractures in postmenopausal women. *Osteoporos Int* 16: 468–474.
19. Nguyen ND, Eisman JA, Nguyen TV. 2006. Anti-hip fracture efficacy of biophosphonates: A Bayesian analysis of clinical trials. *J Bone Miner Res* 21: 340–349.
20. Caro JJ, Ishak KJ, Huybrechts KF, Raggio G, Naujoks C. 2004. The impact of compliance with osteoporosis therapy on fracture rates in actual practice. *Osteoporos Int* 15: 1003–1008.
21. Siris ES, Harris ST, Rosen CJ, Barr CE, Arvesen JN, Abbott TA, Silverman S. 2006. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: Relationship to vertebral and nonvertebral fractures from 2 US claims databases. *Mayo Clin Proc* 81: 1013–1022.
22. Schnitzer T, Bone HG, Crepaldi G, Adami S, McClung M, Kiel D, Felsenberg D, Recker RR, Tonino RP, Roux C, Pinchera A, Foldes AJ, Greenspan SL, Levine MA, Emkey R, Santora AC 2nd, Kaur A, Thompson DE, Yates J, Orloff JJ. 2000. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Alendronate Once-Weekly Study Group. *Aging (Milano)* 12: 1–12.
23. Brown JP, Kendler DL, McClung MR, Emkey RD, Adachi JD, Bolognese MA, Li Z, Balske A, Lindsay R. 2002. The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. *Calcif Tissue Int* 71: 103–111.
24. Cranney A, Guyatt G, Welch V, Griffith L, Adachi JD, Shea B, Tugwell P, Wells G. 2001. A meta-analysis of etidronate for the treatment of postmenopausal osteoporosis. *Osteoporos Int* 12: 140–151.
25. Papapoulos SE, Schimmer RC. 2007. Changes in bone remodelling and antifracture efficacy of intermittent bisphosphonate therapy: Implications from clinical studies with ibandronate. *Ann Rheum Dis* 66: 853–858.
26. Reginster JY, Adami S, Lakatos P, Greenwald M, Stepan JJ, Silverman SL, Christiansen C, Rowell L, Mairon N, Bonvoisin B, Drezner MK, Emkey R, Felsenberg D, Cooper C, Delmas PD, Miller PD. 2006. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. *Ann Rheum Dis* 65: 654–661.
27. Cranney A, Wells GA, Yetisir E, Adami S, Cooper C, Delmas PD, Miller PD, Papapoulos S, Reginster JY, Sambrook PN, Silverman S, Siris E, Adachi JD. 2009. Ibandronate for the prevention of nonvertebral fractures: A pooled analysis of individual patient data. *Osteoporos Int* 20: 291–297.
28. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Caminis J, Tong K, Rosario-Jansen T, Krasnow J, Hue TF, Sellmeyer D, Eriksen EF, Cummings SR; HORIZON Pivotal Fracture Trial. 2007. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 356: 1809–1822.
29. Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, Hyldstrup L, Recknor C, Nordsletten L, Moore KA, Lavecchia C, Zhang J, Mesenbrink P, Hodgson PK, Abrams K, Orloff JJ, Horowitz Z, Eriksen EF, Boonen S; HORIZON Recurrent Fracture Trial. 2007. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 357: 1799–809.
30. Center JR, Bliuc D, Nguyen ND, Nguyen TV, Eisman JA. 2011. Osteoporosis medication and reduced mortality risk in elderly women and men. *J Clin Endocrinol Metab* 96: 1006–1014.
31. Pazianas M, Abrahamsen B, Eiken PA, Eastell R, Russell RGG. 2012. Reduced colon cancer incidence and mortality in postmenopausal women treated with an oral bisphosphonate-Danish National Register based Cohort Study. 2012. *J Bone Miner Res* 23(11): 2693–2701.
32. Sambrook PN, Cameron ID, Chen JS, March LM, Simpson JM, Cumming RG, Seibel MJ. 2011. Oral bisphosphonates are associated with reduced mortality in frail older people: A prospective five-year study. *Osteoporos Int* 22: 2551–2556.
33. Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, Rodriguez-Portales JA, Downs RW, Gupta J, Santora AC, Liberman UA; Alendronate Phase III Osteoporosis Treatment Study Group. 2004. Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med* 350: 1189–1199.
34. Mellström DD, Sörensen OH, Goemaere S, Roux C, Johnson TD, Chines AA. 2004. Seven years of treatment with risedronate in women with postmenopausal osteoporosis. *Calcif Tissue Int* 75: 462–468.
35. Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, Satterfield S, Wallace RB, Bauer DC, Palermo L, Wehren LE, Lombardi A, Santora AC, Cummings SR; FLEX Research Group. 2006. Effects of continuing or stopping alendronate after 5 years of treatment: The Fracture Intervention Trial Long-term Extension (FLEX): A randomized trial. *JAMA* 296: 2927–2938.

36. Black DM, Reid IR, Boonen S, Bucci-Rechtweg C, Cauley JA, Cosman F, Cummings SR, Hue TF, Lippuner K, Lakatos P, Leung PC, Man Z, Martinez R, Tan M, Ruzycky ME, Eastell R. 2012. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: A randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res* 27(2): 243–254.
37. Allen MR, Iwata K, Phipps R, Burr DB. 2006. Alterations in canine vertebral bone turnover, microdamage accumulation, and biomechanical properties following 1-year treatment with clinical treatment doses of risedronate or alendronate. *Bone* 39: 872–879.
38. Chapurlat RD, Arlot M, Burt-Pichat B, Chavassieux P, Roux JP, Portero-Muzy N, Delmas PD, Chapurlat RD, Arlot M, Burt-Pichat B, Chavassieux P, Roux J-P, Portero-Muzy N, Delmas PD. 2007. Microcrack frequency and bone remodeling in postmenopausal osteoporotic women on long-term bisphosphonates: A bone biopsy study. *J Bone Miner Res* 22: 1502–1509.
39. Bauer DC, Black DM, Garnero P, Hochberg M, Ott S, Orloff J, Thompson DE, Ewing SK, Delmas PD; Fracture Intervention Trial Study Group. 2004. Change in bone turnover and hip, non-spine, and vertebral fracture in alendronate-treated women: The fracture intervention trial. *J Bone Miner Res* 19: 1250–1258.
40. Miller PD, Delmas PD, Lindsay R, Watts NB, Luckey M, Adachi J, Greenspan SL, Seeman E, Boonen S, Meeves S, Lang TF, Bilezikian JP. 2008. Early responsiveness of women with osteoporosis to teriparatide after therapy with alendronate or risedronate. *J Clin Endocrinol Metab* 93: 3785–3793.
41. McClung M, Recker R, Miller P, Fiske D, Minkoff J, Kriegman A, Zhou W, Adera M, Davis J. 2007. Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. *Bone* 41: 122–128.
42. Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA, Brown TD, Cheung AM, Cosman F, Curtis JR, Dell R, Dempster D, Einhorn TA, Genant HK, Geusens P, Klaushofer K, Koval K, Lane JM, McKiernan F, McKinney R, Ng A, Nieves J, O'Keefe R, Papapoulos S, Sen HT, van der Meulen MCH, Weinsten RS, Whyte M. 2010. Atypical subtrochanteric and diaphyseal femoral fractures: Report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 25: 2267–2294.
43. Giusti A, Hamdy NAT, Dekkers OM, Ramautar SR, Dijkstra S, Papapoulos SE. 2011. Atypicalfractures and bisphosphonate therapy: A cohort study of patients with femoral fracture with radiographic adjudication of fracture site and features. *Bone* 48: 966–971.
44. Schilcher J, Michaelsson K, Aspenberg P. 2011. Bisphosphonate use and atypical fractures of the femoral shaft. *N Engl J Med* 364: 1728–1737.
45. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, Gagel RF, Gilsanz V, Guise T, Koka S, McCauley LK, McGowan J, McKee MD, Mohla S, Pendrys DG, Raisz LG, Ruggiero SL, Shafer DM, Shum L, Silverman SL, Van Poznak CH, Watts N, Woo SB, Shane E; American Society for Bone and Mineral Research. 2007. Bisphosphonate-associated osteonecrosis of the jaw: Report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 22: 1479–1491.
46. Rizzoli R, Burlet N, Cahall D, Delmas PD, Eriksen EF, Felsenberg D, Grbic J, Jontell M, Landesberg R, Laslop A, Wollenhaupt M, Papapoulos S, Sezer O, Sprafka M, Reginster JY. 2008. Osteonecrosis of the jaw and bisphosphonate treatment for osteoporosis. *Bone* 42: 841–847.
47. Compston J. 2011. Pathophysiology of atypical femoral fractures and osteonecrosis of the jaw. *Osteoporos Int* 22: 2951–2961.
48. Pazianas M, Abrahamsen B. 2011. Safety of bisphosphonates. *Bone* 49: 103–110.
49. Kanis JA, Reginster J-Y, Kaufman J-M, Ringe JD, Adachi JD, Hiligsmann M, Rizzoli R, Cooper C. 2012. A reappraisal of generic bisphosphonates in osteoporosis. *Osteoporos Int* 23: 213–221.
50. Abrahamsen B, Pazianas M, Eiken P, Russell RG, Eastell R. 2012. Esophageal and gastric cancer incidence and mortality in alendronate users. *J Bone Miner Res* 27(3): 679–686.