

Once-yearly zoledronic acid in the prevention of osteoporotic bone fractures in postmenopausal women

Irene Lambrinouadaki
Sophia Vlachou
Fotini Galapi
Dimitra Papadimitriou
K Papadias

2nd Department of Obstetrics
and Gynecology, University of Athens,
Areataieio Hospital, Greece

Abstract: Zoledronic acid is a nitrogen-containing, third-generation bisphosphonate that has recently been approved for the treatment of postmenopausal osteoporosis as an annual intravenous infusion. Zoledronic acid is an antiresorptive agent which has a high affinity for mineralized bone and especially for sites of high bone turnover. Zoledronic acid is excreted by the kidney without further metabolism. Zoledronic acid administered as a 5 mg intravenous infusion annually increases bone mineral density in the lumbar spine and femoral neck by 6.7% and 5.1% respectively and reduces the incidence of new vertebral and hip fractures by 70% and 41% respectively in postmenopausal women with osteoporosis. Most common side effects are post-dose fever, flu-like symptoms, myalgia, arthralgia, and headache which usually occur in the first 3 days after infusion and are self-limited. Rare adverse effects include renal dysfunction, hypocalcemia, atrial fibrillation, and osteonecrosis of the jaw.

Keywords: zoledronic acid, postmenopausal osteoporosis, bisphosphonate

Introduction

Osteoporosis is characterized by low bone mass and abnormal bone quality which lead to decreased bone strength and increased susceptibility to fractures (Consensus Development Conference 1993). According to the World Health Organization (WHO) and the European Foundation for Osteoporosis and Bone Disease (Kanis et al 1997), the definition of osteoporosis is based on the measurement of bone mineral density (BMD) using the T-score. The T-score represents the number of standard deviations from the peak bone mass in healthy adults at the age of 30. Osteoporosis is defined by a T-score equal to or greater than -2.5 , which is the reference point used in clinical trials. Osteopenia is defined by a T-score between -1 and -2.5 . Osteoporosis is one of the most common health problems in postmenopausal women with great socio-economic importance. Using the WHO criteria, 34%–50% of US women >50 years have osteopenia and 17%–20% suffer from osteoporosis (Looker et al 1995; Siris et al 2001).

Bisphosphonates have demonstrated efficacy in reducing vertebral and nonvertebral fracture risk (Lambrinouadaki et al 2006). They are pyrophosphate analogues that have been modified to act as bone-specific anti-resorptive agents by exerting a potent inhibitory effect on osteoclasts. Thus, they reduce bone turnover, increase BMD, and decrease fracture risk both at the lumbar spine and the hip. Bisphosphonates have a high affinity for bone surfaces, where they accumulate, and due to this selectivity of action they lack systemic side-effects. Alendronate and risedronate are administered orally either daily or once weekly, while ibandronate is a newer third-generation bisphosphonate administered once monthly with similar efficacy for BMD and for markers of bone remodeling. The main adverse effect is upper gastrointestinal

Correspondence: Irene Lambrinouadaki
27, Themistokleous Street, Dionysos,
GR-14578, Athens, Greece
Tel +30 210 6410944
Fax +30 210 6410325
Email ilambrinouadaki@hotmail.com

irritation, which together with the strict dosing schedule for oral bisphosphonates, represent major reasons for poor compliance. Therefore, new intravenous (IV) therapies have been developed that allow dosing at very long intervals, which should improve adherence to therapy.

Chemistry

Zoledronic acid is a nitrogen-containing bisphosphonate. Its main structure has a phosphorus-carbon-phosphorus core with a hydroxyl group attached to the R1 position (Green 2001). A heterocyclic imidazole group is attached to the R2 position and differentiates zoledronic acid from other bisphosphonates, concerning the chemical structure (Widler et al 2002).

Mechanism of action

Zoledronic acid is a potent inhibitor of bone resorption. It inhibits osteoclast proliferation (Coxon et al 2000) and induces osteoclast apoptotic cell death (Benford et al 2001). Its potency results from its high affinity for mineralized bone and especially for sites of high bone turnover (Nancollas et al 2006). Zoledronic acid inhibits farnesyl diphosphate (FPP) synthase and in addition the cellular biosynthetic, FPP synthase-mediated mevalonate pathway (Benford et al 2001). In the absence of FPP synthase, FPP and geranylgeranyl diphosphate are not produced, which results in the inhibition of the GTP-binding proteins prenylation in osteoclasts. Low levels of prenylated GTP-binding proteins inhibit osteoclast activity and induce osteoclast apoptosis (Boissier et al 2000; Benford et al 2001; Green 2001). Furthermore, zoledronic acid may boost osteoblast differentiation and increase bone mineralization (Reinholz et al 2000).

Pharmacokinetics

Zoledronic acid is not metabolized in humans and is excreted intact in the urine. It has minor or no effects on the cytochrome P450 enzyme system and therefore has no interaction with the drugs metabolized via cytochrome P450.

Zoledronic acid binding to plasma proteins is 22%. Zoledronic acid concentration in plasma after the infusion decreases rapidly due to the increased absorption of the drug by the bone. However, small amounts of zoledronic acid can be detected in plasma several days after the infusion, representing the drug released gradually from the bone during bone turn-over. In a study of pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with bone metastases (Chen et al 2002), 24 hours after infusion the peak concentrations of zoledronic acid in plasma decreased to <1% of C_{max} .

The excretion of zoledronic acid by the kidney does not depend on the dose or the infusion time (Chen et al 2002). The drug can be detected in urine in trace amounts up to 28 days after the infusion, although adequate amounts are present in urine only in the first 24 hours (Chen et al 2002). The amount found in the urine in the first 24 hours post dose, however, represents just the one- or two-thirds of the total dose as a result of the increased binding of the drug to the bone.

Indications beyond postmenopausal osteoporosis

Zoledronic acid is indicated for the prevention of skeletal-related events (SREs) such as pathological fractures, bone pain, spinal compression, need for bone radiation, or surgery in patients with bone metastases, at a recommended dose of 4 mg IV every 3–4 weeks, and for the treatment of hypercalcemia of malignancy (HCM) at a recommended dose of 4 mg given as a single IV infusion. These malignancies most commonly include prostate cancer, breast cancer, lung cancer, or multiple myeloma (Perry and Figgitt 2004). Patients with recurrent or metastatic prostate cancer often present with bone loss and the androgen deprivation therapy can trigger further rapid BMD decreases (Smith 2006). Intermittent administration of zoledronic acid in these patients increases BMD (Smith et al 2003; Ryan et al 2007), suppresses markers of bone turnover (Ryan et al 2007), and reduces the incidence of pathologic fractures and bone pain (Saad 2002). Zoledronic acid has also been used for the prevention of bone loss and fracture incidence in women with breast cancer receiving estrogen-depleting therapies such as aromatase inhibitors (Hadji 2007). Zoledronic acid improves or stabilizes bone density (Brufsky 2006; Gnani et al 2007) and reduces the frequency of skeletal-related events by 30%–40% (Body 2006). Monthly IV infusions of zoledronic acid have been shown to reduce skeletal complications among patients with multiple myeloma and are now a mainstay of myeloma therapy (Rosen et al 2001; Yeh and Berenson 2006). Treatment with zoledronic acid in Paget's disease improves short-term control of increased bone turnover and maintains a prolonged biochemical remission, making it the most effective therapy available to date (Reid et al 2005; Hosking et al 2007). HCM is among the most common and most serious complications of malignancy in the late stage and occurs in 5%–10% of all cancer patients. Zoledronic acid is effective and well tolerated for hypercalcemia of malignancy in a dose of 4 mg IV (Kenji Kawada et al 2005). The administration of zoledronic acid in cancer patients at intermittent doses of 4 mg is generally well tolerated. Osteonecrosis of the jaw

(ONJ) is a rare complication, mainly seen in combination with other risk factors such as dental surgery or trauma, concurrent glucocorticoids, systemic chemotherapy, local radiation, and malnutrition. This complication is usually observed in cancer patients, probably due to the repeated dosage regimen and the prolonged exposure. The annual dosage regimen used in postmenopausal osteoporosis, on the other hand, is considered safe with regard to the risk of ONJ. In order to minimize the risk a dental evaluation should be conducted before, during and after treatment (Wutzl et al 2006).

Efficacy of zoledronic acid in the treatment of postmenopausal osteoporosis

Many clinical studies up to now have demonstrated the efficacy of the annual intravenous infusion of zoledronic acid with respect to the treatment of postmenopausal osteoporosis.

The indication for postmenopausal osteoporosis was based on the HORIZON Pivotal Fracture Trial (Black et al 2007). This trial included 7765 patients (mean age, 73 years) who were randomly assigned to receive either a single 15-minute infusion of zoledronic acid (5 mg) or placebo at baseline, at 12 months, and at 24 months. The patients were followed until 36 months. Inclusion criteria were lumbar spine BMD T-score less than or equal to -1.5 and at least 2 mild or moderate existing vertebral fracture(s) or a femoral neck BMD T-score less than or equal to -2.5 with or without evidence of existing vertebral fracture(s). Treatment with zoledronic acid reduced the risk of morphometric vertebral fracture by 70% during a 3-year period, compared to placebo (3.3% incidence of morphometric vertebral fracture in the zoledronic acid group compared to 10.9% in the placebo group, relative risk = 0.30, 95% confidence interval [CI] = 0.24–0.38). Additionally, there was a reduction in the risk of hip fracture by 41% (1.4% incidence of hip fracture in the zoledronic acid group and 2.5% in the placebo group, hazard ratio = 0.59, 95% CI = 0.42–0.83). Nonvertebral fractures, clinical fractures, and clinical vertebral fractures were reduced by 25%, 33%, and 77%, respectively ($p < 0.001$ for all comparisons). Patients receiving zoledronic acid had also a significant improvement in BMD and bone metabolism markers. The results of this trial indicate that a once-yearly infusion of zoledronic acid during a 3-year period significantly reduces the risk of vertebral, hip, and other fractures in patients with postmenopausal osteoporosis. However, it should

be taken into account that the HORIZON trial recruited patients who had already sustained a vertebral fracture and were, therefore, a selected high risk population, who might have shown higher rates of fracture reduction compared to patients without prevalent fractures.

A randomized, double-blind, double-dummy, multicenter trial was conducted in order to assess the safety and the efficacy of a single dose of IV zoledronic acid 5 mg compared to oral alendronate 70 mg weekly in postmenopausal women with low BMD who had previously been treated with alendronate (McClung et al 2007). In this trial, a single infusion of zoledronic acid 5 mg maintained BMD 12 months following the switch from oral alendronate in women with osteoporosis. In the zoledronic acid group, mean biomarker levels were reduced from baseline after 3 months, returned to baseline after 6 months, and increased thereafter but remained within the premenopausal range. On the contrary, mean biomarker levels in the alendronate group remained at or close to baseline levels for the duration of the study. The overall rates of adverse events were comparable in both groups. Additionally, bone biopsies indicated that both treatments decrease excessive remodeling seen in osteoporosis. More specifically, 23 specimens with comparable baseline characteristics had adequate tissue for examination. All the specimens had normal appearance and contained adequate double tetracycline label, indicating that remodeling continued with both treating options. There was no evidence of marrow fibrosis and bone tissue appeared normal with no excess accumulation of unmineralized osteoid. The two treatments resulted in almost identical effects on static and dynamic histomorphometric measures. The median point estimates of activation frequency for the groups treated with zoledronic acid and alendronate were 0.08 and 0.09, respectively. This confirms the fact that bone turnover is not excessively reduced with zoledronic acid treatment. As for the preference expressed by the participants, 78.7% of the patients preferred the once-yearly infusion to weekly oral therapy. According to the above, patients can be safely switched from oral alendronate to zoledronic acid 5 mg infusion with maintenance of therapeutic effect for at least 12 months.

In a substudy of the HORIZON pivotal fracture trial (Recker et al 2008) 152 patients receiving intravenous zoledronic acid 5 mg once-yearly underwent bone biopsy in order to determine effects on bone remodelling and bone architecture. According to this study, the zoledronic acid group exhibited higher trabecular bone volume ($p = 0.020$), higher trabecular numbers ($p = 0.008$), decreased trabecular separation ($p = 0.011$), and a trend toward improvement in

connectivity density ($p = 0.062$) compared to the placebo group, all indicating better preservation of trabecular structure after treatment with zoledronic acid. Bone biopsies also indicate that zoledronic acid is associated with reduced bone turnover due to the fact that it causes reduction in activation frequency and also in mineralizing surface and volume referent bone formation rate versus placebo. Additionally, mineral appositional rate was improved in the zoledronic acid group ($p = 0.0002$) suggesting improved osteoblast function. Finally, zoledronic acid is associated with normal osteoid formation and mineralization of newly formed bone as indicated by the similar mineralization lag time in both groups and the lower osteoid volume ($p < 0.0001$) and osteoid thickness ($p = 0.0094$) in zoledronic acid-treated patients. According to the above, zoledronic acid favors the reduction of bone turnover and the preservation of bone structure and mass without any signs of adynamic bone.

A randomized, double-blind, double-dummy, multicenter, 24-week trial (Saag et al 2007) evaluated the onset of action for both zoledronic acid and alendronate comparing a single infusion of zoledronic acid 5 mg ($n = 69$) to weekly oral alendronate 70 mg ($n = 59$) in postmenopausal women with low BMD (T-score ≤ -2 by DXA) as assessed by reductions in urine N-telopeptide of type I collagen (NTX) at week 1. Zoledronic acid resulted in a significantly greater reduction in urine NTX levels at week 1 compared to alendronate, suggesting a more rapid onset of action ($p < 0.0001$).

At week 1, 6 patients receiving zoledronic acid and 0 patients receiving alendronate had NTX levels below the limit of detection. The zoledronic acid group had significantly lower mean urine NTX values throughout the 24-week study, compared to the alendronate group. The lowest levels of mean urine NTX was at 1 week in the zoledronic group. Levels gradually increased thereafter, and remained stable within the study reference range for premenopausal women from week 12 to study end. In the alendronate group, mean urine NTX levels showed a more gradual reduction, reaching the lowest levels by week 12. At week 24, 1 patient in the zoledronic acid group and 0 patients in the alendronate group had NTX below the limit of detection. Reductions in serum C-terminal telopeptide of type I collagen (β -CTX) levels over time were similar to those observed for urine NTX. Zoledronic acid resulted in significantly greater reductions in serum β -CTX levels at all post-baseline time points compared to alendronate. At week 24, mean β -CTX was within the premenopausal reference range in the alendronate group and slightly below the reference range in the zoledronic acid

group. Additionally, the decline of serum beta-C-telopeptide of type I collagen (β -CTX) levels was greater for zoledronic acid in comparison with alendronate throughout the 24-week study, with levels remaining in the premenopausal range from week 12 to the end of the study. Additionally, bone-specific alkaline phosphatase (BSAP) levels showed a more gradual reduction in both groups, reaching premenopausal range by week 12. According to this trial, a single infusion of zoledronic acid 5 mg leads to a greater and more rapid reduction in bone resorption markers compared to oral alendronate 70 mg, although they both have similar effects on bone formation.

A 1-year, randomized, double-blind, placebo-controlled trial by Reid et al included 351 postmenopausal women with low BMD who received placebo or 5 regimens of intravenous zoledronic acid (0.25 mg, 0.5 mg, or 1 mg at 3-month intervals or a total annual dose of 4 mg or 2 doses of 2 mg each, 6 months apart) (Reid et al 2002). The aim was to assess the effect of zoledronic acid on bone turnover and BMD. The increase in BMD was similar in all the zoledronic acid groups and ranged between 4.3% and 5.1% and between 3.1% and 3.5% for the femoral neck compared to placebo. Biochemical markers of bone resorption were significantly suppressed throughout the study in all zoledronic acid groups. According to this trial, annual infusions of zoledronic acid might be an effective treatment for postmenopausal osteoporosis, as they produce effects on bone turnover and bone density as great as those achieved with daily oral bisphosphonates with proven efficacy against fractures.

A 5-year study by Devogelaer et al assessed the long-term efficacy and safety of prolonged use of zoledronic acid 4 mg for over 5 years (Devogelaer et al 2007). A single infusion of zoledronic acid 4 mg given once-yearly for 2, 3 or 5 years was well tolerated with no evidence of excessive bone turnover reduction or any safety signals. Moreover, BMD increased significantly, while bone turnover markers decreased from baseline and were maintained within premenopausal reference ranges.

The HORIZON recurrent fracture trial evaluated the fracture recurrence and mortality in patients receiving zoledronic acid (Lyles et al 2007). In this trial 1065 patients were assigned to receive yearly 5 mg of intravenous zoledronic acid, and 1062 patients were assigned to receive placebo. The infusions were first administered within 90 days after surgical repair of a hip fracture. The aim was to evaluate the impact of zoledronic acid on new clinical fractures and the mortality after hip fracture. The rates of any new clinical fracture were 8.6% in the zoledronic acid group and 13.9%

in the placebo group, indicating a 35% risk reduction with zoledronic acid. The respective rates of a new clinical vertebral fracture were 1.7% and 3.8%, and the respective rates of new nonvertebral fractures were 7.6% and 10.7%. Concerning mortality there was a 28% reduction in deaths from any cause in the zoledronic acid group ($p = 0.01$). According to this study an annual infusion of zoledronic acid within 90 days after repair of a low-trauma hip fracture was associated with a reduction in the rate of new clinical fractures and with improved survival.

Adverse events

In the HORIZON pivotal fracture trial no significant differences were observed with respect to the serious adverse events between patients receiving zoledronic acid and placebo, while most adverse events were mild to moderate. The incidence of all-cause mortality was 3.4% in the zoledronic acid group and 2.9% in the placebo group. A once-yearly infusion of zoledronic acid during a 3-year period was associated with a significant and sustained decrease in the risk of vertebral, hip and other fractures (Black et al 2007). Taking that fractures are an important cause of disability and mortality among postmenopausal women, the use of zoledronic acid for treatment of postmenopausal osteoporosis is associated with improved survival (Lyles et al 2007). The incidence of serious adverse events in this trial was 30.1% and 29.2% for the zoledronic acid group and the placebo group respectively.

A statistically significant higher rate of atrial fibrillation was recorded in the zoledronic acid group compared to placebo (1.3% and 0.5%, respectively). More women who received zoledronic acid intravenously developed serious atrial fibrillation compared to women who received placebo (Black et al 2007). However, the rates of all incidents of atrial fibrillation (serious plus nonserious) were not significantly different between groups treated with zoledronic acid versus placebo. FDA (United States Food and Drug Administration) has reviewed the data about the possible association between zoledronic acid and atrial fibrillation and has not been able to identify a population of zoledronic acid users at increased risk for atrial fibrillation. Additionally, most incidents of this disorder take place more than 1 month after the infusion of the drug, by which time zoledronic acid is undetectable in the circulation. Also, in a subset of patients who were monitored by electrocardiogram up to the 11th day after infusion, there was no significant difference in the prevalence of atrial fibrillation between patients who received zoledronic acid and those who

received placebo. Until now, FDA has not decided how these data on atrial fibrillation should be interpreted and recommends that healthcare practitioners and patients should not change their prescribing practices on the use of zoledronic acid.

Zoledronic acid has been mainly associated with some postdose symptoms, including fever (18.1%), myalgia (9.4%), flu-like symptoms (7.8%), arthralgia (6.8%), and headache (6.5%) (Black et al 2007). The above symptoms occur more often within the first 3 days following zoledronic acid infusion, are mild and resolve within 3 days of the event onset. The above postdose symptoms can be reduced with the administration of acetaminophen or ibuprofen shortly after zoledronic acid infusion.

ONJ is a rare adverse event of zoledronic acid treatment which appears to occur more frequently with intravenous bisphosphonates compared to the oral regimens (Krueger et al 2007). The majority of the reported cases, however, were also receiving chemotherapy or corticosteroids. Furthermore, this adverse effect has been associated with invasive dental procedures, such as root canal or dental extraction. According to a retrospective study its prevalence in patients receiving bisphosphonates intravenously was 1 in 71.5. The review of 1951 medical records led to the identification of 2 patients with ONJ who had received bisphosphonates. Both patients treated with bisphosphonates had multiple myeloma and were receiving monthly infusions (Murad et al 2007). In a prospective evaluation of 252 cancer patients treated with bisphosphonates for 6 years the incidence of ONJ was 6.7% overall, 9.9% in myeloma 6.5% in prostate cancer and 2.9% in breast cancer. The median number of infusions was 35 in the patients who developed ONJ compared with 15 for patients without ONJ ($p < 0.001$) (Bamias et al 2005). As noted previously, length of exposure seems to be the most important risk factor for this adverse event and caution is required for use of bisphosphonates beyond 2 years (Body 2006). Kut et al, assessing the risk of this complication in oncologic patients, reported a prevalence of 1.5% (Kut et al 2004). In the Pivotal Fracture Trial (Black et al 2007) 7736 patients with postmenopausal osteoporosis were examined. Only 1 patient treated with zoledronic acid and 1 patient treated with placebo developed symptoms consistent with ONJ, which resolved after appropriate treatment.

Other adverse events associated with zoledronic acid include local reactions at the infusion site such as itching, redness and/or pain which have been reported in 0.7% of patients receiving zoledronic acid intravenously (Black et al

2007). Additionally, 0.2% of patients treated with zoledronic acid developed iritis, uveitis, episcleritis (Black et al 2007).

Zoledronic acid has been associated with renal dysfunction manifested as deterioration of renal function (increased serum creatinine) and in rare cases acute renal failure. In the HORIZON pivotal fracture trial, 1.8% of patients receiving zoledronic acid developed renal dysfunction, compared to 0.8% in the placebo group. Severe renal dysfunction was rarely reported. In the same trial, 0.2% of the patients receiving zoledronic acid, primarily after the first dose, developed a mild, asymptomatic decrease in calcium levels (less than 1.87 mmol/L). Hypocalcemia is usually asymptomatic, but symptoms may include numbness or tingling sensations, especially in the area around the mouth, muscle spasms or muscle cramps.

Practice guidelines

The recommended dose for the treatment of postmenopausal osteoporosis is 5 mg of zoledronic acid in 100 mL ready to infuse solution. It is administered intravenously via a vented infusion line. The infusion time must not be less than 15 minutes and the infusion rate should be constant. On the day of the infusion, patients may eat and drink normally. It is recommended that they drink at least 2 glasses of water (500 mL), before and after the infusion of zoledronic acid. Appropriate hydration is of great importance especially in patients receiving diuretic therapy.

Serum calcium levels and vitamin D levels should be assessed before treatment with zoledronic acid. Additionally, renal function should be assessed and creatinine should be measured before treatment. It is also recommended that patients with possible risk factors (eg, cancer, chemotherapy, head and neck radiotherapy, corticosteroids, poor oral hygiene) should be subjected to a routine dental examination with appropriate preventive dentistry in order to avoid the rare possibility of ONJ.

It is strongly advised that patients treated with zoledronic acid receive adequate calcium and vitamin D supplementation especially in the days before and following the infusion. In the HORIZON pivotal fracture trial, patients received 1000–1500 mg of elemental calcium as well as 400–1200 IU of vitamin D supplements per day.

Contraindications refer to patients with hypersensitivity to this drug, or to any bisphosphonate or component of the container. Zoledronic acid is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min), in pregnant women, nursing mothers and in patients with noncorrected hypocalcemia at the time of infusion.

Patients receiving zoledronic acid should not be treated with other bisphosphonates concomitantly.

Disclosures

The authors have no conflicts of interest to disclose.

References

- Bamias A, Kastritis E, Bamia C, et al. 2005. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. *J Clin Oncol*, 23:8580–7.
- Benford HL, McGowan NW, Helfrich MH, et al. 2001. Visualization of bisphosphonate-induced caspase-3 activity in apoptotic osteoclasts in vitro. *Bone*, 28:465–73.
- Black DM, Delmas PD, Eastell R, et al; HORIZON Pivotal Fracture Trial. 2007. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*, 356:1809–22.
- Body J. 2006. Breast cancer: Bisphosphonates therapy for metastatic bone disease. *Clin Cancer Res*, 12:6258–63.
- Boissier S, Ferreras M, Peyruchaud O, et al. 2000. Bisphosphonates inhibit breast and prostate carcinoma cell invasion, an early event in the formation of bone metastases. *Cancer Res*, 60:2949–54.
- Brufsky A. 2006. Management of cancer-treatment-induced bone loss in postmenopausal women undergoing adjuvant breast cancer therapy: a Z-FAST update. *Semin Oncol*, 33:13–17.
- Chen T, Berenson J, Vescio R, et al. 2002. Pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with bone metastases. *J Clin Pharmacol*, 42:1228–36.
- Consensus Development Conference. 1993. Diagnosis, prophylaxis and treatment of osteoporosis. *Am J Med*, 94:646–50.
- Coxon FP, Helfrich MH, Van't Hof R, et al. 2000. Protein geranylgeranylation is required for osteoclast formation, function, and survival: Inhibition by bisphosphonates and GGTI-298. *J Bone Miner Res*, 15:1467–76.
- Devogelaer JP, Brown JP, Burckhardt P, et al. 2007. Zoledronic acid efficacy and safety over five years in postmenopausal osteoporosis. *Osteoporos Int*, 18:1211–18.
- Geusens PP, Lems WF. 2007. Fracture prevention in postmenopausal women with osteoporosis by an annual infusion of zoledronic acid. *Ned Tijdschr Geneesk*, 151:1445–8.
- Gnant MF, Mlineritsch B, Luschin-Ebengreuth G, et al; Austrian Breast and Colorectal Cancer Study Group. 2007. Zoledronic acid prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: a report from the Austrian Breast and Colorectal Cancer Study Group. *J Clin Oncol*, 25:820–8.
- Green JR. 2001. Chemical and biological prerequisites for novel bisphosphonate molecules: Results of comparative preclinical studies. *Semin Oncol*, 28(Suppl 6):4–10.
- Green JR. 2002. Preclinical pharmacology of zoledronic acid. *Semin Oncol*, 29:3–11.
- Hadji P. 2007. Reducing the risk of bone loss associated with breast cancer treatment. *Breast*, 16S3:10–15.
- Hosking D, Lyles K, Brown JP, et al. 2007. Long-term control of bone turnover in Paget's disease with zoledronic acid and risedronate. *J Bone Miner Res*, 22:142–8.
- Kanis JA, Delmas P, Burckhardt P, et al. for the European Foundation for Osteoporosis and Bone Disease. 1997. Guidelines for diagnosis and treatment of osteoporosis. *Osteoporos Int*, 7:390–406.
- Kenji Kawada, Hironobu Minami, Keniichi Okabe, et al. 2005. A Multi-center and Open Label Clinical Trial of Zoledronic Acid 4 mg in Patients with Hypercalcemia of Malignancy. *Jpn J Clin Oncol*, 35:28–33.
- Krueger CD, West PM, Sargent M, et al. 2007. Bisphosphonate-induced osteonecrosis of the jaw. *Ann Pharmacother*, 41(2):276–84.
- Kut V, Mehta J, Tariman J, et al. 2004. Osteonecrosis of the jaw in Myeloma Patients Receiving Pamidronate or Zoledronate. *Blood*, 104:4933.

- Lambrinoudaki I, Christodoulakos G, Botsis D. 2006. Bisphosphonates. *Ann N Y Acad Sci*, 1092:397–402.
- Li EC, Davis LE. 2003. Zoledronic acid: a new parenteral bisphosphonate. *Clin Ther*, 25:2669–708.
- Looker AC, Johnston CC Jr, Wahner HW, et al. 1995. Prevalence of low mineral bone density in older U.S. women from NHANES III. *J Bone Miner Res*, 10:796–802.
- Lyles KW, Colón-Emeric CS, Magaziner JS, et al; HORIZON Recurrent Fracture Trial. 2007. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med*, 357:1799–809.
- McClung M, Recker R, Miller P, et al. 2007. Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. *Bone*, 41:122–8.
- Murad OM, Arora S, Farag AF, et al. 2007. Bisphosphonates and osteonecrosis of the jaw: a retrospective study. *Endocr Pract*, 13:232–8.
- Nancollas GH, Tang R, Phipps RJ, et al. 2006. Novel insights into actions of bisphosphonates on bone: differences in interactions with hydroxyapatite. *Bone*, 38:617–27.
- Perry CM, Figgitt DP. 2004. Zoledronic acid: a review of its use in patients with advanced cancer. *Drugs*, 64:1197–211.
- Recker RR, Delmas PD, Halse J, et al. 2008. The effects of intravenous zoledronic acid once yearly on bone remodeling and bone structure. *J Bone Miner Res*, 23:6–16.
- Reid IR, Brown JP, Burckhardt P, et al. 2002. Intravenous zoledronic acid in postmenopausal women with low bone mineral density. *N Engl J Med*, 346:653–61.
- Reid IR, Miller P, Lyles K, et al. 2005. Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. *N Engl J Med*, 353:898–908.
- Reinholz GG, Getz B, Pederson L, et al. 2000. Bisphosphonates directly regulate cell proliferation, differentiation, and gene expression in human osteoblasts. *Cancer Res*, 60:6001–7.
- Rosen LS, Gordon D, Antonio BS, et al. 2001. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer J*, 7:377–87.
- Ryan CW, Huo D, Bylow K, et al. 2007. Suppression of bone density loss and bone turnover in patients with hormone-sensitive prostate cancer and receiving zoledronic acid. *BJU Int*, 100:70–5.
- Saad F. 2002. Zoledronic acid significantly reduces pathologic fractures in patients with advanced-stage prostate cancer metastatic to bone. *Clin Prostate Cancer*, 1:145–52.
- Saag K, Lindsay R, Kriegman A, et al. 2007. A single zoledronic acid infusion reduces bone resorption markers more rapidly than weekly oral alendronate in postmenopausal women with low bone mineral density. *Bone*, 40:1238–43.
- Siris ES, Miller PD, Barrett-Connor E, et al. 2001. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: Results from the National Osteoporosis Risk Assessment. *JAMA*, 286:2815–22.
- Smith MR, Eastham J, Gleason D, et al. 2003. Randomized controlled trial of zoledronic acid to prevent bone loss in men undergoing androgen deprivation therapy for nonmetastatic prostate cancer. *J Urol*, 169:2008–12.
- Smith MR. 2006. Treatment-related osteoporosis in men with prostate cancer. *Clin Cancer Res*, 12:6315–19.
- World Health Organization. Prevention and management of osteoporosis. WHO Technical Report Series 921 [online]. URL: http://whqlibdoc.who.int/trs/WHO_TRS_921.pdf.
- Widler L, Jaeggi KA, Glatt M, et al. 2002. Highly potent geminal bisphosphonates. From pamidronate disodium (Aredia) to zoledronic acid (Zometa). *J Med Chem*, 45:3721–38.
- Wutzl A, Eisenmenger G, Hoffmann M, et al. 2006. Osteonecrosis of the jaws and bisphosphonate treatment in cancer patients. *Wien Klin Wochenschr*, 118:473–8.
- Yeh HS, Berenson JR. 2006. Treatment for myeloma bone disease. *Clin Cancer Res*, 12:6279–84.

