Zoledronic acid in the management of osteoporosis: the HORIZON trials

Zoledronic acid 5 mg is an annually administered intravenous bisphosphonate that is approved for the treatment of osteoporosis. The Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly (HORIZON) Pivotal Fracture trial showed an increase in bone mineral density, decrease in bone turnover markers, and significant reduction in the risk of vertebral, hip and other fractures in women with postmenopausal osteoporosis treated over a period of 3 years. The HORIZON Recurrent Fracture Trial demonstrated that an annual infusion of zoledronic acid started within 90 days of surgical repair of a low-trauma hip fracture in women and men was associated with a significant decrease in the risk of new clinical fractures and an increase in survival. The tolerability and safety profile of treatment in both studies was generally favorable, with the most common adverse event being transient flu-like symptoms shortly after infusion.

KEYWORDS: bisphosphonates, fractures, osteoporosis, treatment, zoledronate, zoledronic acid

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Osteoporosis is a skeletal disease characterized by low bone mineral density (BMD) and poor bone quality that reduces bone strength and increases the risk of fractures [1]. It is a worldwide public health problem with serious consequences in terms of personal suffering and costs to society [2,3]. Approximately 30% of postmenopausal Caucasian women have osteoporosis [4], with a lifetime fracture risk of 40% [5]. Fractures of the hip and spine are associated with increased morbidity and mortality [6,7]. Despite the general availability of clinical tools to diagnose osteoporosis and predict the risk of fractures [8], patients who could benefit from treatment to reduce fracture risk are commonly not recognized or treated [9]. When patients are started on a pharmacological therapy for osteoporosis, compliance is poor [10]. Typically, less than 50% of patients are still taking the drug 1 year after it is prescribed [11]. It has been demonstrated that patients who are compliant to therapy have a greater increase in BMD [12], lower fracture risk [13] and reduced healthcare costs [10] compared with those who are not compliant. The US Surgeon General has identified poor compliance and persistence to therapy as a major obstacle in the treatment of osteoporosis, and suggested that less frequent dosing and simplified drug administration be considered as a potential means to improve adherence [14].

Drugs for the treatment of osteoporosis are classified as antiresorptive (anticatabolic) or anabolic (bone-building) [15], depending on their predominant effect on bone remodeling. Estrogens, bisphosphonates (e.g., alendronate, risedronate, ibandronate and zoledronic acid), calcitonin and raloxifene are antiresorptive agents that strengthen bone by decreasing bone turnover. This results in stabilization or an increase in BMD by reducing the remodeling space and prolonging secondary mineralization. Bone microarchitecture is preserved, with a reduction in trabecular perforation and decrease in cortical porosity. Recombinant human parathyroid hormone, PTH(1-34) (teriparatide) and PTH(1-84), are anabolic drugs that strengthen bone and reduce fracture risk by increasing bone formation. They are associated with an increase in bone size and restoration or formation of new trabecular microarchitectural elements. Strontium ranelate (approved in some countries for the treatment of osteoporosis) may have both antiresorptive and anabolic properties. Although all of these drugs have been shown to reduce the risk of fractures in women with postmenopausal osteoporosis, each has limitations as well. Oral bisphosphonates have complex administration requirements (fasting, ingestion with plain water only and post-dose fasting) and have been associated with upper gastrointestinal symptoms when used in clinical practice. Intravenous (iv.) bisphosphonates (ibandronate and zoledronic acid) must be given by trained staff in a physician's office or infusion center. Estrogen and raloxifene are associated with non-skeletal risks (e.g., thromboembolic events), as

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well as nonskeletal benefits, such as reduction in hot flashes with estrogen and decreased risk of invasive breast cancer with raloxifene. Nasal calcitonin is usually well tolerated, but may cause nasal congestion, burning or bleeding in some patients. Teriparatide involves daily self-administered subcutaneous injection, and is higher in cost than the other agents. Recent trends in the development of drugs for the treatment of postmenopausal osteoporosis (PMO) have been toward injectable dosing with long dosing intervals, with the goal of maximizing compliance and persistence to effective and safe therapy.

The most recent bisphosphonate to be approved for the treatment of PMO is iv. zoledronic acid 5 mg every 12 months (also known as zoledronate; Reclast® in the USA, Aclasta® in other countries, Novartis Pharmaceutical Corporation, NJ, USA) (Figure 1). It is also approved to reduce the incidence of new clinical fractures in patients at high risk of fracture, defined as a recent low-trauma hip fracture, and for the treatment of Paget's disease of the bone. Zoledronic acid 5 mg iv. given annually for the treatment of osteoporosis should not be confused with zoledronic acid 4 mg (Zometa®, Novartis Pharmaceutical Corporation) iv., which is given with a much shorter dosing interval (often every 3–4 weeks) and far greater cumulative dosage for cancer-related conditions (hypercalcemia of malignancy, bone metastases associated with solid tumors and multiple myeloma). This is a review of two clinical trials evaluating the efficacy and safety of zoledronic acid 5 mg every 12 months for the treatment of osteoporosis – the Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly (HORIZON) Pivotal Fracture Trial [16] and the HORIZON Recurrent Fracture Trial [17].

HORIZON Pivotal Fracture Trial

Design

The HORIZON Pivotal Fracture Trial was a 3-year, Phase III, international, multicenter, randomized, double-blind, placebo-controlled clinical trial evaluating the efficacy and safety of zoledronic acid in women with postmenopausal osteoporosis. Patients were randomly assigned to once-yearly treatment with a 15-min infusion of either zoledronic acid 5 mg or placebo given at baseline, month 12 and month 24. All participants received daily calcium (1000–1500 mg) and vitamin D (400–1200 IU). Patients were seen at clinic visits at months 6, 12, 24 and 36, and contacted quarterly for telephone interviews.

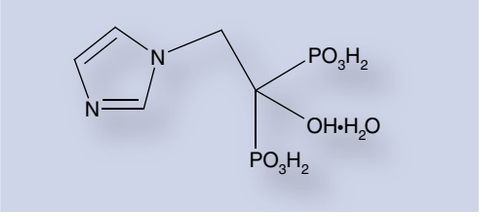

Figure 1. Zoledronic acid.

Study population

Postmenopausal women between the ages of 65 and 89 years were eligible for participation in the study if they had a BMD T-score of -2.5 or less at the femoral neck (i.e., a densitometric diagnosis of osteoporosis) or a T-score of -1.5 or less with radiological evidence of at least two mild or one moderate vertebral fracture (i.e., a clinical diagnosis of osteoporosis). Previous use of oral bisphosphonates was allowed, provided a prespecified washout period was attained. Concomitant use of the following bone-active agents was allowed at baseline and during the study: hormone therapy, raloxifene, calcitonin, tibolone, tamoxifene, dehydroepiandrosterone, ipriflavone and medroxyprogesterone. Patients were not eligible for participation if there was any previous use of parathyroid hormone, strontium ranelate or sodium fluoride; use of anabolic steroids or growth hormone within 6 months of study entry; or use of oral or iv. glucocorticoids in the previous 12 months. Patients with abnormal serum calcium levels (>2.75 mmol/l or <2.00 mmol/l) or abnormal renal function (calculated creatinine clearance <30 ml/min or urine dipstick showing >2+ protein) were excluded. Patients were divided into two strata:

- Stratum 1 patients were taking no osteoporosis medications at the time of randomization
- Stratum 2 patients were taking an allowed osteoporosis medication.

Efficacy end points

There were two primary end points: new morphometric vertebral fractures in Stratum 1 and hip fractures in Stratum 1 and Stratum 2. Secondary end points included any nonvertebral fracture, any clinical fracture and clinical vertebral fracture; BMD change at the lumbar spine, femoral neck and total hip; and changes in bone turnover markers – serum C-telopeptide of type 1 collagen (a marker of bone resorption) and bone-specific alkaline phosphatase (a marker of bone formation). Vertebral fractures were diagnosed with lateral spine radiographs carried out at baseline, and at months 12, 24 and

36 or early termination for those in Stratum 1, and at baseline, month 36 or early termination for Stratum 2. Vertebral fractures were defined according to quantitative morphometry and standard methods [18]. BMD was measured by dual-energy x-ray absorptiometry (DXA) at baseline and at months 6, 12, 24 and 36.

Assessment of safety

All adverse events and serious adverse events were recorded and categorized according to standard coding procedures. Renal safety was evaluated in a subgroup of patients by measuring serum creatinine 9–11 days after each infusion. Cardiac safety was measured in another subgroup with 12-lead electrocardiograms before and 9–11 days after the third infusion. Adjudication or expert review was conducted for several categories of adverse events, including osteonecrosis of the jaw (ONJ), ocular events, hypocalcemia, renal events and incomplete fracture healing.

Data analysis

All statistical analyses were prespecified. The primary efficacy end points were new vertebral and hip fractures over 3 years. Safety analyses included all patients who received at least one infusion.

Results

The study population consisted of 7765 women randomized to receive zoledronic acid (n = 3889) or placebo (n = 3876). The mean age was 73 years, with approximately half from Europe and half from North and South America and Asia. At 3 years, zoledronic acid significantly reduced the relative risk of morphometric vertebral fracture by 70% (3.3 vs 10.9%; $p < 0.001$ vs placebo) (Figure 2) and hip fracture by 41% (1.4 vs 2.5%; $p = 0.002$ vs placebo) (Figure 3). Zoledronic acid also significantly reduced the incidence of clinical vertebral fractures by 77% (0.5 vs 2.6%), nonvertebral fractures by 25% (8.0 vs 10.7%), and all clinical fractures by 33% (8.4 vs 12.8%) ($p < 0.001$ for all comparisons). In the zoledronic acid group, BMD increased significantly at the total hip (6.02%; 95% confidence interval [CI]: 5.77–76.28), lumbar spine (6.71%; 95% CI: 5.69–7.74), and femoral neck (5.06%; 95% CI: 4.76–5.36) compared with the placebo group ($p < 0.001$ for all comparisons). There was a significant reduction in levels of all bone turnover markers in the zoledronic acid group compared with placebo.

Zoledronic acid was generally well tolerated, with the most common adverse events consisting of mild-to-moderate, post-dose, flu-like symptoms that have also been observed with other iv. bisphosphonates. These generally resolved within 3 days of onset and declined markedly with subsequent infusions. There were no spontaneous reports of ONJ, a rare event that has been described in patients taking bisphosphonates, most often for malignant conditions [19]. One patient in the zoledronic acid group and one in the placebo group had delayed wound healing in the maxillofacial region that was classified as potential ONJ; both of these events resolved following antibiotic therapy and limited debridement. Atrial fibrillation as a serious adverse event occurred more frequently in those treated with zoledronic acid (50 vs 20 patients, $p < 0.001$), although the overall risk of atrial fibrillation was similar in both groups. A significant increase in risk of atrial

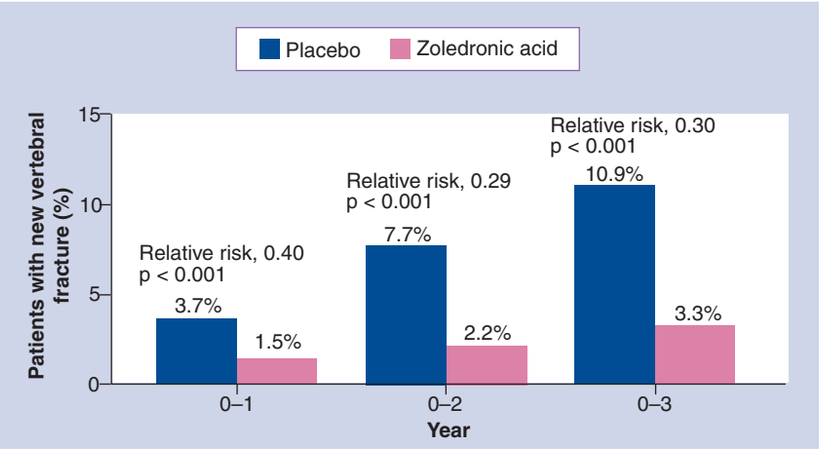

Figure 2. Relative risk of morphometric vertebral fracture in the HORIZON Pivotal Fracture Trial. Reproduced with permission from [16]. Copyright © 2007 Massachusetts Medical Society. All rights reserved.

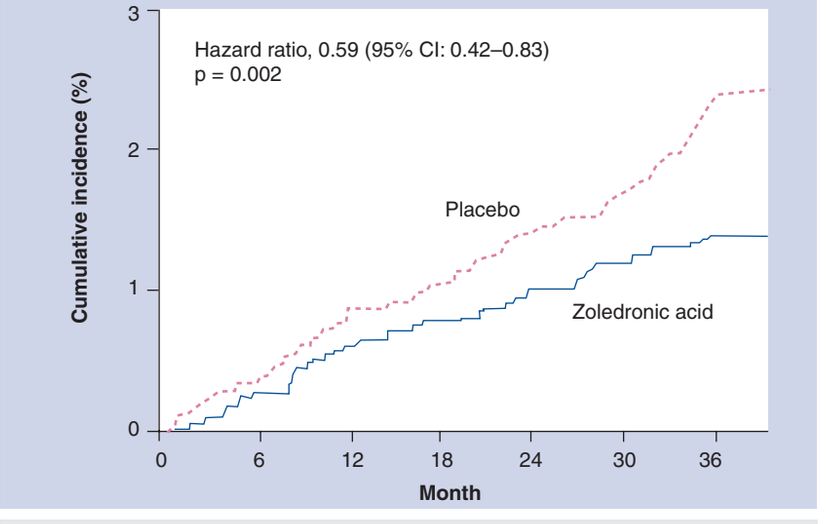

Figure 3. Cumulative incidence of hip fracture in HORIZON Pivotal Fracture Trial. Data shown are for Stratum 1 (no concurrent osteoporosis therapy) + Stratum 2 (concurrent osteoporosis medications taken). Reproduced with permission from [16]. Copyright © 2007 Massachusetts Medical Society. All rights reserved.

fibrillation has not been observed in other prospective randomized clinical trials with zoledronic acid, or in studies of other bisphosphonates. The data are mixed on recent retrospective observational studies, with one showing an increase in the risk of atrial fibrillation [20] and another showing no increase in risk [21]. No systematic rise in calculated creatinine clearance was observed over 3 years. Small, transient elevations in serum creatinine were observed within 10 days of dosing in 1.8% of zoledronic acid-treated patients, compared with 0.8% of placebo-treated patients; these events resolved without specific therapy, and all zoledronic acid patients received the next scheduled dose. No long-term renal effects of zoledronic acid were observed, with similar renal function profiles reported for zoledronic acid and placebo groups after 3 years of therapy.

Conclusion

Zoledronic acid 5 mg iv. every 12 months over 3 years was associated with a significant decrease in the risk of vertebral, hip and other fractures in women with PMO. It was generally well-tolerated, with the most common adverse event being transient flu-like symptoms, primarily seen after the first infusion.

HORIZON Recurrent Fracture Trial

Design

The HORIZON Recurrent Fracture Trial was a Phase III, international, multicenter, randomized, double-blind, placebo-controlled clinical trial evaluating the efficacy and safety of zoledronic acid in women and men with a recent low-trauma hip fracture. Patients were randomly assigned to once-yearly treatment with a 15-min infusion of either zoledronic acid 5 mg or placebo, with the first dose given within 90 days of surgical repair of the fracture and continued every 12 months for the duration of the study. In patients with a baseline serum 25-hydroxyvitamin D level of 15 ng/ml or less, or if the level was not available, a loading dose of vitamin D (50,000–125,000 IU of vitamin D2 or D3 orally or intramuscularly) was given prior to the first infusion of the study drug. Thereafter, all participants received daily calcium (1000–1500 mg) and vitamin D (800–1200 IU). Patients were seen at clinic visits at months 6, 12, 24 and 36, and contacted quarterly for telephone interviews.

Study population

Women and men age 50 years and older with a recent surgical repair of a low-trauma hip fracture, who were ambulatory prior to the hip fracture, were eligible for participation in the study. Concomitant use of nasal calcitonin, selective estrogen receptor modulators, hormone replacement, tibolone and external hip protectors were allowed at the discretion of the investigator. Patients were excluded for conditions that included a calculated creatinine clearance of less than 30 ml/min, corrected serum calcium level of more than 2.8 mmol/l or less than 2.0 mmol/l, metabolic bone disease other than osteoporosis and life expectancy of less than 6 months.

Efficacy end points

The primary end point was new clinical fracture, excluding fractures of the face, fingers, toes, and those occurring in abnormal bone (e.g., metastatic bone disease). Secondary end points included clinical vertebral fractures and change in BMD in the nonfractured hip.

Assessment of safety

All adverse events and serious adverse events were recorded and categorized according to standard coding procedures. Adjudicated review was conducted for several categories of adverse events, including ONJ, ocular events, hypocalcemia, renal events, delayed fracture healing and cardiac arrhythmias recorded as a serious adverse event.

Data analysis

The duration of the trial was event-driven, with an estimated 211 clinical fractures required to achieve a power of 90%. A two-sided level of significance of 0.05 was needed to detect 35% reduction in the rate of clinical fracture in the zoledronic acid group compared with the placebo group. Two interim analyses with prespecified stopping rules were planned.

Results

A total of 2127 patients were randomized, with 1065 assigned to receive zoledronic acid (76.7% female, 23.3% male, mean age: 74.4 years) and 1062 assigned to receive placebo (75.5% female, 24.5% male, mean age: 74.6 years). The median follow-up time was 1.9 years, with 71.3% of patients completing the trial. A total of 424 new clinical fractures occurred in 231 patients. Compared with placebo, the zoledronic acid group had a significantly reduced risk of clinical fracture (35%; 8.6 vs 13.9%; p = 0.001), clinical vertebral fracture (46%; 1.7 vs 3.8%; p = 0.02) and nonvertebral fracture (27%, 7.6 vs 10.7%; p = 0.03) (Figure 4). Zoledronic acid also produced progressively larger increases in total hip and femoral neck BMD throughout the course of

the trial (12, 24 and 36 months), compared with decreases from baseline at each time point among placebo recipients ($p < 0.001$ for all comparisons). Zoledronic acid patients had a 28% lower mortality risk compared with those receiving placebo infusions. This is the first time such a benefit has been reported for an osteoporosis medication.

The most frequent adverse events in patients receiving zoledronic acid were transient post-infusion symptoms such as pyrexia, myalgia, bone and musculoskeletal pain. No cases of ONJ were reported, and the rates of renal and cardiovascular adverse events, including atrial fibrillation and stroke, were similar in the two groups. There were no adverse effects on fracture healing.

Conclusion

Zoledronic acid 5 mg iv. started within 90 days of surgical repair of low trauma hip fracture and continued every 12 months was associated with a reduction in the rate of new clinical fractures, a significant decrease in mortality and favorable safety profile.

Future perspective

US FDA-approved medications for the treatment of PMO include oral alendronate, oral risedronate, oral and iv. ibandronate, iv. zoledronic acid, oral raloxifene, intranasal calcitonin and subcutaneous teriparatide. Other drugs (e.g., etidronate, tibolone, strontium ranelate and PTH [1–84]) are approved in some countries. The proven benefit of these drugs in terms of fracture risk reduction is attenuated by generally poor compliance and persistence that has been reported in many studies. This is a particular concern with the oral bisphosphonates, the first-line therapy for most patients with PMO, due to the complexity of administration being greater than with most of the other therapeutic options. Longer dosing intervals (weekly and monthly vs daily) for oral bisphosphonates have improved patient acceptance and have been associated with improved, but still suboptimal, adherence to therapy.

Bisphosphonates given intravenously offer some advantages over intermittent oral dosing. Patients may find the very long dosing intervals, particularly every 12 months with zoledronic acid, more convenient than the shorter intervals with oral dosing, and therefore be more likely to continue treatment. Recalling patients for an annual visit may be more successful than trusting that patients take medication regularly and correctly at home throughout the year, thereby providing an opportunity to improve compliance to therapy. Intravenous dosing is a helpful therapeutic option for those with gastrointestinal intolerance, malabsorption or contraindications to oral bisphosphonates. Bioavailability is 100% (compared with less than 1% with oral bisphosphonates), thereby obviating the concern of diminished therapeutic effect in patients taking oral bisphosphonates incorrectly. The data showing reduction in fracture risk with zoledronic acid is very robust, and the long-term safety profile appears good.

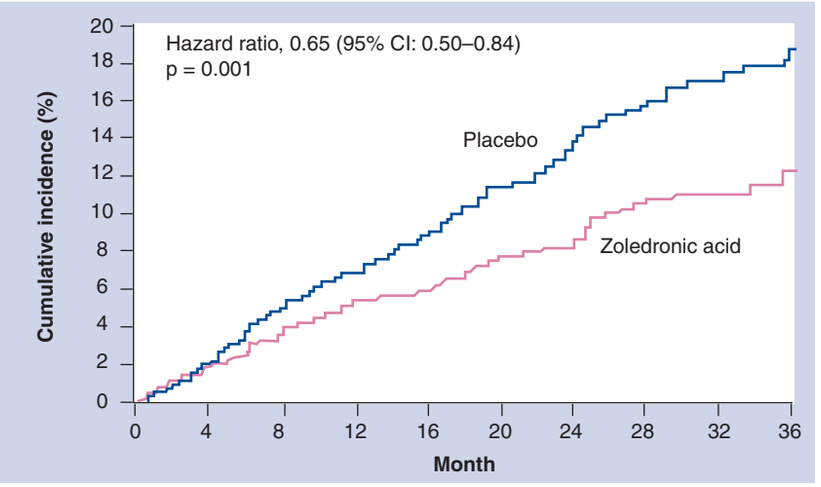

Figure 4. Cumulative incidence of clinical fractures in the HORIZON Recurrent Fracture Trial. Reproduced with permission from [17].

Intravenous bisphosphonates are associated with potential disadvantages as well. Since most primary care physicians do not administer iv. drugs in the office, referral to an osteoporosis specialist or infusion center may be necessary. This creates a bureaucratic barrier for some physicians, who might find it easier to simply write a prescription for an oral medication. The cost of iv. bisphosphonates is higher than oral bisphosphonates, especially when generic alendronate is considered. Although a single dose of zoledronic acid 5 mg provides a guarantee of adherence to therapy for the following 12 months, the rate of return for subsequent injections is not currently known. If the return rate for repeat injections is sufficiently high, the benefits of fracture risk reduction may at least partially offset the cost differential with other agents that are less expensive, but associated with poor adherence and lower antifracture effect. As with any osteoporosis medication, optimal response may in part depend on recognition and treatment of secondary causes of osteoporosis, and patient cooperation by means of a healthy lifestyle, avoidance of smoking and excess alcohol and adequate intake of calcium and vitamin D.

While all patients with PMO are potential candidates for treatment with iv. zoledronic acid, those who are being considered must be appropriately evaluated. In addition to assessment

of all factors contributing to skeletal fragility, serum calcium and creatinine must be measured prior to each infusion. Zoledronic acid should not be given to those with uncorrected hypocalcemia or severe renal impairment (creatinine clearance <35 ml/min). All patients who receive zoledronic acid should have adequate calcium (at least 1200 mg per day) and vitamin D (800–1000 IU of vitamin D3 per day) intake [22]. Some patients may need a higher vitamin D intake to achieve a desirable serum 25-hydroxyvitamin D level. It should not be given to patients also receiving other bisphosphonates, including zoledronic acid 4 mg (Zometa®, Novartis).

Over the next 5 years, development of medications for the treatment of osteoporosis will continue to focus on convenient methods of administration and infrequent dosing intervals as a means of maximizing adherence to therapy. The potential benefits of combining a bisphosphonate (sequentially, concomitantly or cyclically) with an anabolic agent (e.g., teriparatide, PTH [1–84], or others in development) will be further explored. Other drugs, such as denosumab, a fully human monoclonal antibody to receptor activator for nuclear factor-κB ligand given by subcutaneous injection every 6 months, may become available. The future clinical utility of zoledronic acid for the treatment of osteoporosis is promising, with ongoing investigations likely to provide a better understanding of its full potential. Zoledronic acid, with a very long dosing interval of 1 year, is likely to play a continuing role in the class of bisphosphonate therapy.

Financial & competing interests disclosure

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Executive summary

Mechanism of action

- Zoledronic acid is a nitrogen-containing bisphosphonate that inhibits osteoclast formation, activity and survival.
- Its principal metabolic action is inhibition of the mevalonate pathway by inhibiting farnesyl pyrophosphate synthase, resulting in decreased synthesis of farnesyl pyrophosphate and geranylgeranyl pyrophosphate, which are necessary for prenylation of small guanosine triphosphate-binding proteins in osteoclasts.

Pharmacokinetic properties

- After intravenous (iv.) administration, zoledronic acid produces dose-proportional plasma concentrations that decline rapidly in a multiphasic manner.
- Approximately 60% of administered dose binds to mineralized bone, with the remainder rapidly excreted by the kidneys.

Clinical efficacy

- Zoledronic acid 5 mg iv. every 12 months is associated with an increase in bone mineral density (BMD), reduction in bone turnover markers and decreased rates of vertebral fracture, hip fracture and other fractures compared with placebo in women with postmenopausal osteoporosis.
- Zoledronic acid 5 mg iv. every 12 months, started within 90 days of surgical repair of low-trauma hip fracture in women and men over age 50 years, is associated with increased BMD, reduced rate of clinical fractures and a decrease in mortality compared with placebo.

Safety & tolerability

- The most common adverse event consists of transient flu-like symptoms, such as pyrexia, bone and muscle pain, which are more likely to occur after the first injection, especially in bisphosphonate-naïve patients, than with subsequent injections.
- Osteonecrosis of the jaw has been reported with zoledronic acid and other bisphosphonates, primarily in patients treated for cancer-related conditions in doses much larger than that used for osteoporosis.
- Zoledronic acid should not be given to women who are pregnant, nor to patients with hypocalcemia or severe renal impairment (creatinine clearance <35 ml/min).
- All patients receiving zoledronic acid should be adequately supplemented with calcium and vitamin D.

Drug interactions

- There are no known drug interactions, although caution is advised when zoledronic acid is used with agents associated with hypocalcemia, such as aminoglycosides or loop diuretics.
- Caution is advised when zoledronic acid is used with agents that are potentially nephrotoxic, such as nonsteroidal anti-inflammatory drugs, around the time of infusion.

Dosage & administration

- Zoledronic acid 5 mg iv. for the treatment of osteoporosis is given over at least 15 min every 12 months.

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