Clinical Medicine Reviews in Women's Health

REVIEW

Zoledronic Acid: Efficacy of Single-Dose 2-year Protection Against Postmenopausal Osteoporosis

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Abstract: Postmenopausal osteoporosis is a disease associated with increased morbidity and mortality. Oral bisphosphonates administered once weekly are associated with adverse events from the upper gastrointestinal system, leading to poor adherence. Zoledronic acid is a nitrogen-containing third-generation bisphosphonate approved for the treatment of postmenopausal osteoporosis. It is a potent antiresorptive agent which expresses high affinity for the hydroxyapatite of the bone and accumulates at sites of increased bone turnover. Adverse events include fever, flu-like symptoms, myalgia, arthralgia, and headache, while rare adverse effects include hypocalcemia, renal dysfunction, atrial fibrillation, and osteonecrosis of the jaw. The drug is excreted intact through kidneys. Until recently, the recommended dosage was 5 mg given as an annual intravenous infusion. In 2009, intravenous zoledronic acid 5 mg was approved for the treatment of postmenopausal osteoporosis as a single infusion every two years. This review summarizes all evidence supporting the efficacy of a single biennial 5 mg dose against postmenopausal osteoporosis. The FDA approval was based on a clinical randomized trial which included osteopenic postmenopausal women and showed that BMD in all measured sites remained increased 24 months after the infusion. Many studies showed similar results concerning BMD and also demonstrated that bone turnover markers remained suppressed for >12 months. The less frequent administration of zoledronic acid is expected to improve adherence and decrease the adverse events, leading subsequently to improved clinical results.

Keywords: postmenopausal osteoporosis; zoledronic acid; bone turnover; efficacy

Clinical Medicine Reviews in Women's Health 2010:2 25–36

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Introduction

Osteoporosis is a progressive bone disease that associates with increased morbidity and mortality. Bone mass along with bone quality are compromised leading to decreased bone strength and eventually to increased fracture risk.[1] The fracture risk increases 1.5- to 3-fold as bone mineral density (BMD) decreases by 1 standard deviation (SD).[2] The standard method to screen for osteoporosis is dual-energy X-ray absorptiometry (DXA), which measures BMD. Low BMD is considered a risk factor for fractures. Therefore, DXA should be considered in women ≥65 and men ≥70 regardless of risk factors and in younger postmenopausal women and men aged 50–69 years who have clinical risk factors. Additionally, women at menopausal transition should also be examined with DXA in the presence of certain risk factors such as low body weight, previous fracture or the intake of medications which affect bone mass. DXA is mandatory when an individual is a candidate for osteoporosis treatment and for monitoring treatment efficacy. Following the discontinuation of estrogen therapy, postmenopausal women should also be evaluated with DXA.[3]

According to the World Health Organization (WHO), the diagnosis 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 young adults of the same sex and age. Therefore, osteoporosis is defined as T-score ≤2.5 standard deviations below the adult mean value. Osteopenia is defined by a T-score between −1 and −2.5 SD.[4]

Many risk factors contribute to the development of osteoporosis. Peak bone mass is achieved by the age of 25–30 and is followed by a gradual bone loss which is genetically determined and is around 1% annually. Beyond the genetic component, lifestyle is of great importance. Malnutrition including low intake of calcium and Vitamin D, increased alcohol consumption, smoking as well as the lack of exercise predispose to osteoporosis. Additional risk factors are the use of medications that cause bone loss, e.g. corticosteroids as well as the presence of amenorrhea or early menopause.[2] Postmenopausal women experience a higher annual rate of bone loss (4%), which may lead to a 40% bone mass loss between 40–70 years.[5]

The prevalence of osteoporosis among women over 65 years old varies between 26%–50%, depending on age.[3] According to Melton et al[6] the lifetime risk of a woman over 50 to experience a fragility fracture is 40%, compared to a man of the same age who has 13% risk. A vertebral fracture increases long term morbidity in women.[2] Hip fractures are also a common and life-threatening consequence of osteoporosis. It is estimated that 3 months after a hip fracture mortality increases 2.8- to 4-fold. Within a year only 30% regain optimal function, while 50% become disabled and 10–20% die.[7] Additionally, if the patient remains bedridden, complications such as urinary tract infections, pneumonia and decubitus ulcers may also occur.[3]

Osteoporotic fractures have, therefore, physical, psychological and socio-economic consequences. For more accurate screening, a fracture risk algorithm (FRAX) is available on the internet which calculates the 10-year probability for sustaining an osteoporotic fracture, based on risk factors such as BMD, age, smoking, alcohol consumption, body mass index, corticosteroid use, history of previous personal or parental fracture and rheumatoid arthritis.[1,8]

The treatment of osteoporosis includes preventive strategies, such as weight-bearing exercise, adequate protein, calcium and vitamin D intake, as well as cessation of smoking. Antiresorptive therapy, as represented by nitrogen-containing bisphosphonates, is considered as a first line therapy for the treatment of osteoporosis and the reduction of osteoporotic fracture risk.[9,10]

The purpose of the present study was to review the safety and efficacy of bisphosphonates for the treatment of postmenopausal osteoporosis, aiming at a more detailed presentation of the intravenous infusion of zoledronic acid. English literature was reviewed from 1992 via pubmed using key words related to osteoporosis definition, prevalence, monitoring and associated complications, with emphasis on postmenopausal osteoporosis. Clinical study results deriving mostly from double-blind, placebo-controlled studies, with clinically relevant endpoints and appropriate study methodology were reviewed. More specifically, the results of five randomized clinical trials in addition to the results of one randomized controlled study which was followed by two consecutive

open-label extension studies are presented to support the safety and efficacy of the annual zoledronic acid infusion for the treatment of postmenopausal osteoporosis. The most recent FDA approval for the biennial zoledronic acid infusion was based on a randomized, multi-center, double-blind, placebo-controlled trial. Zoledronic acid's prolonged efficacy is also supported by two other randomized controlled trials, two observational studies and an observational extension of a randomized controlled trial.

Bisphosphonates

Bone is a constantly active tissue. The purpose of its continuous remodeling is to adjust to mechanical loading, to repair damages and to maintain the homeostasis of calcium and phosphorus. Bone remodeling is the result of the balanced interplay between osteoclasts (bone-absorbing cells) and osteoblasts (bone formation cells). Osteoclasts degrade old bone every 2–4 weeks, creating a resorption lacuna. Osteoblasts fill this lacuna with newly synthesized osteoid, the extracellular organic matrix, which is consequently mineralized. This bone formation phase lasts 4–6 months and is followed by a resting phase.[2]

Bisphosphonates were introduced to clinical practice almost 20 years ago and are considered first-line therapy for osteoporosis. Pharmacologically, the structure is characterized by two phosphorus groups attached to a carbon atom (P-C-P structure), in addition to the R1 and R2 groups attached to the carbon's two other bonds. This particular structure allows bisphosphonates to remain intact during their interaction with osteoclasts.[9] Additionally, the differences in the R2 chain determine the bone binding affinities of each bisphosphonate.[11]

Depending on the presence of a nitrogen atom, bisphosphonates are classified as non-nitrogen-containing (e.g. clodronate, etidronate) and nitrogen-containing (e.g. alendronate, risedronate, ibandronate, zoledronic acid). Bisphosphonates are bone specific agents that exert their anti-resorptive activity through their strong inhibitory effect on osteoclasts. More specifically, after binding on bone surfaces, bisphosphonates are internalized into the osteoclasts and inhibit bone resorption.

The non-nitrogen-containing bisphosphonates, which are considered less potent, accumulate into osteoclasts and are metabolized to toxic nonhydrolyzable ATP analogues leading to cell apoptosis.[11,12] On the contrary, the more effective nitrogen-containing bisphosphonates interfere with protein prenylation by preventing farsenyl diphosphate synthase.[12,13] Monkkonen et al[14] demonstrated that the inhibition of FPP synthase in the mevalonate pathway by the nitrogen-containing bisphosphonates leads to the accumulation of an upstream metabolite, called isopentenyl pyrophosphate (IPP) and finally to the formation of a pro-apoptotic ATP analog (ApppI). Although the apoptosis of the osteoclasts is the principal antiresoptive effect of nitrogen-containing bisphosphonates, it is not considered their sole mechanism of action.[15]

Nitrogen-containing bisphosphonates are characterized by a primary (aledronate) or tertiary nitrogen (ibandronate) or a nitrogen-containing heterocyclic ring (e.g. zoledronic acid and risedronate). The most strong inhibitor of farnesyl diphosphate synthase is zoledronic acid, followed by risedronate and ibandronate.[16] Further to their inhibitory action on the osteoclasts, bisphosphonates interfere with osteoblastic activity. Bisphosphonates potentiate bone marrow stromal cell proliferation and differentiation thus assisting bone formation.[5] Additionally, they promote the production of osteoprotegerin by the osteoblasts which counteracts RANKL and subsequently suppresses bone resorption.[17] Bisphosphonates establish, thus, a lower balance of bone turnover, analogous to the premenopausal state. This is indicated by the lower levels of bone turnover markers, such as the bone collagen breakdown products CTX (cross-linked C-telopeptide) and NTX (N-telopeptide).[9,18–22]

Once weekly administered oral bisphosphonates are alendronate and risedronate. Once monthly administered oral bishposphonates are ibandronate and risedronate. The effect of ibandronate on bone mineral density and markers of bone remodeling is similar to this of daily alendronate and risedronate.[23] The major problem regarding oral bisphosphonates is adherence. This term defines the extent to which patients adapt to treatment recommendations. Additionally, it refers to persistence i.e. the actual time between the initiation and discontinuation of treatment.[24] It is of great concern that, according to the WHO, adherence to medication in chronic diseases reaches only 50%.[25] Regarding osteoporosis,

poor adherence has been associated with lower suppression of bone turnover markers, lower benefit with respect to BMD and consequently inadequate protection against fracture.[26–28]

Due to their high affinity for bone tissue, bisphosphonates have no systemic effects.[29,23] Their main adverse events, however, are from the upper gastrointestinal (GI) system, mainly gastroesopahgeal reflux, oesophagitis, gastritis and peptic ulcers. The patient shall, therefore, stay in an upright position (standing or sitting) for at least 30 minutes after drug intake. Additionally, the strict dosing schedule of the oral bisphosphonates represents another major reason for inadequate compliance. Provided that poor adherence leads to inadequate clinical benefit, simplifying dosing is a promising strategy. The once weekly administered bisphosphonates are pharmacologically equivalent to the daily administered ones and have been associated with better adherence.[11,30–32] On the other hand, the monthly administered ibandronate has not been clearly associated with better adherence.[33] Upper GI adverse events are similar between ibandronate and alendronate, but flu-like and myoskeletal symptoms are more frequent with ibandronate.[34] Except for the adverse events, oral bisphosphonates are characterized by poor bioavailabilty and it is crucial that the administration takes place on an empty stomach with ≥8 fluid oz (237 ml) tap water to enhance its absorption.[11,9]

In order to avoid the inconveniences deriving from the use of oral bisphosphonates, new intravenous (IV) therapies have been developed that allow dosing at very long intervals which, hopefully, will improve adherence to therapy. Quarterly IV ibandronate (3 mg ibandronate intravenously every 3 months) was approved in 2006 and its efficacy and safety were found similar to that of the oral monthly regimen. The most recently approved bisphosphonate for IV administration is zoledronic acid. The primary indications for the use of intravenous zoledronic acid were hypercalcemia and skeletal complications of malignancy.[35,36] Studies in osteopenic and osteoporotic postmenopausal women, however, have shown that the annual IV use of 5 mg zoledronic acid reduced bone turnover markers more quickly and more intensely compared to 70 mg per week of oral alendronate.[37] Therefore, following the concordant results of many studies, the annual IV zoledronic acid regimen (5 mg/year) was approved in 2007 for use in postmenopausal osteoporosis.[38]

Zoledronic Acid

Chemistry

Zoledronic acid belongs to the nitrogen-containing bisphosphonates. It has a phosphorus-carbon-phosphorus core with a hydroxyl group attached to the R1 position.[39] Regarding its chemical structure, the heterocyclic imidazole group attached to the R2 position differentiates zoledronic acid from other bisphosphonates.[40]

Mechanism of action

Zoledronic acid expresses a potent antiresorptive action, which is mediated through its high affinity for mineralized bone and especially for sites of high bone turnover.[41] Zoledronic acid inhibits the proliferation of the osteoclasts and induces their apoptosis.[42,43]

Zoledronic acid exerts its actions mainly by inhibiting the farnesyl pyrophosphate (FPP) synthase, an enzyme involved in the cellular biosynthetic mevalonate pathway.[43] Zoledronic acid is considered the most potent inhibitor of FFP synthase.[44] The direct effect is the inhibition of isoprenoid lipids synthesis, such as FFP and geranylgeranyl diphosphate (GGPP), which are necessary for the GTP-binding protein prenylation in osteoclasts. The loss of prenylated GTP-binding proteins has been associated with inhibition of osteoclast activity and induction of osteoclast apoptosis.[45,39,43] According to Benford,[43] the apoptosis of the osteoclasts is possibly attributed to the activation of caspase-3-like proteases along with morphological changes and to the loss of mitochondrial membrane integrity. Furthermore, zoledronic acid may enhance osteoblast differentiation[46] with no interference with bone mineralization.[39]

Pharmacokinetics

Zoledronic acid is administered as 5 mg intravenous solution during a period of at least 15 minutes. The patients must be well hydrated before the intravenous infusion, especially if they receive diuretic drugs. Additionally, they must receive the recommended for postmenopausal osteoporosis daily dosage of calcium (at least 1200 mg) and vitamin D (800–1200 IU). The medication is not metabolized in humans and almost 40% of the IV dose is excreted intact in the urine. The remaining 60% binds to the bone due to its high

affinity for this tissue. The binding level to plasma proteins is 22%. Immediately after infusion, there is a rapid elimination from the systemic circulation, due to the increased absorption of the drug by the bone, followed by a longer elimination phase with a half-life of 146 hours.[47] It is noteworthy that less than 1% of the peak concentration observed at the end of the infusion can be traced 24 hours after the injection.[48] The small amounts of the drug detected in plasma several days after the infusion represent the drug which is gradually released from the bone during bone turnover. Zoledronic acid has minor or no effect on the cytochrome P450 enzyme system and does not affect the metabolic clearance of substances metabolized via cytochrome P450.[47]

The excretion of zoledronic acid by the kidney is independent of the dose or the infusion time and the drug can be detected in urine in trace amounts even 28 days after the infusion. The affinity of zoledronic acid for the bone tissue is so potent that the amount of the drug traced in the urine in the first 24-hour represents only the one or two-thirds of the total dose.[47] In the presence of mild or moderate renal impairment (Cl_{Cr}= 50–80 ml/min and Cl_{Cr} = 35–50 ml/min respectively) dose adjustments are not considered necessary.[48] Boonen et al[49] investigating the renal safety of zoledronic acid administered for postmenopausal osteoporosis reported that renal function in the treated women was not affected compared to placebo. However, due to the lack of adequate data, the use of zoledronic acid is not recommended in elderly patients with $Cl_{Cr} \leq 30$ ml/min.[48]

Zoledronic acid in the treatment of postmenopausal osteoporosis: efficacy of a single dose every two years

Zoledronic acid 5 mg was approved in 2007 for the treatment of postmenopausal osteoporosis as a single annual infusion.[38] The approval of zoledronic acid for the treatment of postmenopausal osteoporosis was based on the HORIZON PFT (Pivotal Fracture Trial).[38] This was a double-blind, placebo-controlled, multicenter trial which included 7765 patients (mean age 73 years) and investigated the anti-fracture efficacy of a single annual dose of zoledronic acid 5 mg during a 3-year period. Inclusion criteria were lumbar spine T-score ≤ -1.5 and at least two mild or moderate existing vertebral fractures or a femoral neck T-score ≤ -2.5 with or without evidence of existing vertebral fracture. Zoledronic acid reduced the risk of morphometric vertebral fracture by 70% compared to placebo (3.3% in the zoledronic acid versus 10.9% in the placebo group, $P < 0.001$). The hip fracture rate was 1.4% in the zoledronic acid group compared to 2.5% in the placebo group, representing a 41% relative risk reduction ($P = 0.002$). In addition, non-vertebral fractures, clinical fractures, and clinical vertebral fractures were reduced by 25%, 33%, and 77% respectively ($P < 0.001$ for all comparisons). BMD was also increased in the zoledronic acid group by 6.0%, 6.7% and 5.1% in the total hip, lumbar spine and femoral neck respectively compared to placebo. Nevertheless, it should be taken into account that the HORIZON trial included high risk population, who might have shown higher rates of fracture reduction compared to patients without prevalent fractures.

A separate placebo-controlled trial, the HORIZON-RFT (Recurrent Fracture Trial), investigated the fracture recurrence and mortality in patients with a history of hip fracture receiving zoledronic acid.[50] Infusion of zoledronic acid occurred within 90 days after surgical repair of the hip fracture. The results indicated a 35% risk reduction for any new clinical fracture in the treated group: 8.6% experienced a new clinical fracture in the zoledronic acid group as compared to 13.9% in the placebo. Additionally, the rates of new clinical vertebral fractures were 1.7% and 3.8% and those of new non-vertebral fractures 7.6% and 10.7% in the zoledronic acid and placebo groups respectively. Finally, the rate of new hip fractures was 2.0% in the zoledronic acid group and 3.5% in the placebo group, representing a 30% risk reduction. Regarding the all-cause mortality, there was a 28% reduction in deaths in the zoledronic acid group ($P = 0.01$).

Recker et al[51] evaluated the effects of zoledronic acid on bone remodelling and architecture in a substudy of the HORIZON trial. Bone biopsies of 152 patients receiving intravenous zoledronic acid 5 mg annually showed 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

($P = 0.062$) in the zoledronic acid group compared to placebo. Additionally, there was a reduction in bone turnover due to reduction in activation frequency, in mineralizing surface and in volume referent bone formation rate ($P < 0.0001$). Mineral appositional rate was also improved in the zoledronic acid group. ($P = 0.0002$) Finally, zoledronic acid was associated with normal osteoid formation and mineralization of newly formed bone. The above results strongly suggest that zoledronic acid reduces bone turnover and preserves bone structure and mass.

McClung et al[52] evaluated the safety and efficacy of zoledronic acid versus oral biphosphonate therapy. This randomized, double-blind, multicenter trial was conducted to assess the safety and efficacy of a single IV dose of zoledronic acid 5 mg in comparison with weekly oral alendronate 70 mg in postmenopausal women with low BMD, who were previously on weekly alendronate for at least 1 year prior to randomization. BMD levels were stable for 12 months following the switch from oral alendronate to zoledronic acid in women with osteoporosis. Bone turnover markers, were reduced from baseline after 3 months, returned to baseline after 6 months, and increased thereafter ranging within the premenopausal levels. On the contrary, mean biomarker levels in the group receiving alendronate remained around baseline levels throughout the study. The aggregate rates of adverse events were similar in both groups. Bone biopsies were also evaluated in this study and the results indicated that zoledronic acid and alendronate decreased excessive remodelling without suppressing it. Additionally, there was no observation of marrow fibrosis and there was no excess accumulation of unmineralized osteoid. Finally, 78.7% of the patients expressed their preference for the annual infusion. The study results suggested that patients can be safely switched from oral alendronate to IV zoledronic acid 5 mg and maintain the achieved therapeutic effect for at least 12 months.

Annual IV zoledronic acid and weekly alendronate were also compared regarding the onset of their action in a randomized, double-blind, double-dummy, multicenter trial of 24 weeks duration.[37] The population consisted of postmenopausal women with low BMD (T score ≤ -2) and the onset of action was assessed using the reductions in urine N-telopeptide of type I collagen (NTX) at week 1. Zoledronic acid was characterized by a more rapid onset of action as it resulted in a significantly higher reduction in urine NTX at week 1 compared to alendronate ($P < 0.0001$). Additionally, the zoledronic acid group had significantly lower mean urine NTX values during the 24-week study. Furthermore, zoledronic acid resulted in significantly higher reduction of serum β-CTX (beta-C-telopeptide of type I collagen) levels throughout the study compared to aledronate. Finally, bone-specific alkaline phosphatase was reduced in a gradual manner in both groups, reaching premenopausal range by week 12. Conclusively, annual IV zoledronic acid 5 mg causes a steeper decrease of a higher magnitude in bone resorption markers compared to oral alendronate 70 mg, while both have a similar effect on bone formation.

Devogelaer et al[53] conducted a 5 year study in order to assess the efficacy and safety of prolonged use of zoledronic acid 4 mg. Annual infusions of zoledronic acid for 2, 3 or 5 years resulted in not excessively reduced bone turnover. Additionally, it was well tolerated and devoid of safety issues. Bone turnover markers decreased from baseline and remained in the premenopausal reference ranges, while BMD was significantly increased.

In May 2009, FDA approved the use of a single IV infusion of zoledronic acid 5 mg every two years in postmenopausal osteoporosis.[54] Studies have shown prolonged efficacy of the regimen, beyond 12 months.[55] This advantage is attributed to the extremely high affinity of zoledronic acid to the hydroxyapatite of the bone tissue. After the accumulation of zoledronic acid on the bone surface, the formation of new bone leads to the internalization of the drug, which nevertheless remains active due to the constant bone remodelling. Therefore, the drug is remobilized and re-localized to the bone surface, maintaining its action for months and years.[56] Adherence is expected to be higher due to the less frequent administration. Additionally, the lower risk of adverse events along with the cost reduction will allow more patients to receive zoledronic acid treatment.

A 50% cost reduction results from the switch to biennial administration of zoledronic acid for postmenopausal osteoporosis compared to annual dosage. The cost-effectiveness of zoledronic acid is even more evident when it is compared to oral bisphosphonates administered weekly for the same period.[57]

The economic benefit arising from the less frequent administration of zoledronic acid is very promising taking that postmenopausal osteoporosis is a chronic disease which requires long-term monitoring.

The approval of the biennial regimen was based on a randomized, double-blind, multicenter study which included 581 osteopenic postmenopausal women over 45 years old in early (<5 years) or late (>5 years) menopause. The primary endpoint was BMD values after 2 years compared to baseline. Three groups of patients were investigated. In the first group postmenopausal women received zoledronic acid at baseline and again after one year, while in the second group women received zoledronic acid at baseline and placebo at one year. Finally, in the third group women received placebo both at baseline and at one year. The results showed that zoledronic acid given as a single dose increased BMD at lumbar spine by 6.3% and 5.4% in the early and late menopause group respectively after two years compared to placebo (both $P < 0.001$).[55]

According to Grey et al[58] the antiresorptive effects of a single IV infusion of zoledronic acid remain for at least two years. Results in osteopenic postmenopausal women concerning both BMD and bone turnover markers are comparable between 12 and 24 months. Lumbar spine BMD was higher by 5.7% (95% CI: 4.0–7.4) after two years in the zoledronic acid group compared to placebo ($P < 0.0001$). Similarly, BMD at proximal femoral was increased by 3.9% (95% CI: 2.2–5.7) in the zoledronic acid group compared to placebo ($P < 0.0001$). Moreover, total body BMD was 1.7% (95% CI: 0.8–2.5) higher in the zoledronic group ($P < 0.0001$). Bone turnover was assessed by measuring β-CTX and NTX for bone resorption and P1NP and osteocalcin for bone formation. The mean levels of all four markers remained decreased by at least 38% throughout the study ($P < 0.0001$ for each marker). These findings indicate that the anti-fracture efficacy of zoledronic acid may persist until 24 months after infusion.

The prolonged efficacy of a single 5 mg infusion of zoledronic acid has been suggested by many studies which investigated osteopenic patients with diseases causing low bone mass, apart from postmenopausal osteoporosis. Bolland et al[59] conducted a study in HIV-infected men with osteopenia and reported that two years after the second of two annual zoledronic acid 4 mg infusions BMD increased, while bone turnover markers remained decreased. At all time points, bone turnover markers were lower in the zoledronic acid group and the levels of urine N-telopeptide, serum C-telopeptide and osteocalcin did not differ significantly between 12 and 24 months. BMD in all measurement sites increased in the zoledronic acid group and its values did not vary significantly between 12 and 24. It is noteworthy that in this study CTX levels between 12 and 24 months were similar to those of postmenopausal women receiving annual infusions of zoledronic acid 5 mg.[38]

The efficacy of a single infusion of zoledronic acid 4 mg beyond 12 months was also evaluated in a study which included both female and male patients with low BMD. The measurement of bone turnover markers at 18 months after the infusion revealed that both CTX-I and BSAP remained decreased compared to baseline values ($P = 0.009$ and $P = 0.02$ respectively). However, serum CTX, which was decreased by 66% at 12 months, was only 41% below baseline value at 18 months, reflecting a possible partial loss of effect. On the other hand, bone-specific alkaline phosphatase (BSAP) was 31% and 27% below baseline value at 12 and 18 months respectively, compared to baseline. Additionally, BMD was increased at 18 months compared to 12 months (6.1% in lumbar spine and 2.0% in total hip).[60]

According to a study evaluating the efficacy of a 4 mg single dose of zoledronic acid in osteopenic cancer patients, BMD at lumbar spine increased by 3.1% at 12 months, 5.2% at 24 months and 5.3% at 36 months compared to baseline values ($P < 0.001$). Additionally, BMD at hip increased by 2.7%, 3.5% and 4.3% at 12, 24 and 36 months respectively ($P < 0.001$). It is noteworthy that three years after the infusion increases in BMD compared to baseline at both spine and hip were observed in 84% and 90% of the participants. Additionally, serum NTX decreased by 42%, 33% and 31% at 12, 24 and 36 months, respectively ($P < 0.001$). Conclusively, zoledronic acid exhibits a prolonged antiresorptive effect on BMD beyond 12 months after a single infusion.[56] Furthermore, Hosking et al[61] evaluated the long term efficacy of zoledronic acid compared to oral risedronate in patients with Paget's disease. Contrarily to risedronate, zoledronic acid led to a stabilization of mean levels of ALP at the middle of the reference

range. All bone turnover markers were unchanged during 18 months of follow-up.

Indications beyond postmenopausal osteoporosis

The first indication of zoledronic acid was the treatment of malignancy—associated hypercalcemia, mainly in patients with prostate cancer, breast cancer, lung cancer or multiple myeloma.[62] Furthermore, zoledronic acid prevents manifestations such as pathological fractures, bone pain and spinal compression so that the need for bone radiation or surgery could be avoided. Specifically, metastatic prostate cancer may be associated with bone loss, which is also enhanced by the androgen deprivation therapy.[63] In these cases, zoledronic acid acts effectively by increasing BMD,[64,65] by reducing bone turnover markers,[66] while it protects from pathologic fractures and bone pain.[66] The recommended dosage is 4 mg intravenously (IV) every 3 to 4 weeks.

Regarding breast cancer, zoledronic acid reduces bone loss and prevents fractures in women receiving estrogen depleting therapies, such as aromatase inhibitors.[67] In addition, monthly IV infusions of zoledronic acid are a first-line therapy for the skeletal manifestations of multiple myeloma.[68,69] Hypercalcemia of malignancy (HCM) is encountered in the final stages of malignancies in 5–10% of all cancer patients and is treated with 4 mg intravenous infusions of zoledronic acid with a frequency depending on the underlying disease and patient response.[70] Additionally, zoledronic acid is considered crucial for the treatment of Paget's disease, as it maintains bone turnover in the desirable range.[61]

Recently, intravenous zoledronic acid 5 mg administered once annually has been approved for the prevention and treatment of glucocorticoid-induced osteoporosis. It is indicated for both men and women who initiate or continue systemic glycocorticoid therary of at least 7.5 mg prednisone per day (or equivalent) and who must remain on this regimen for at least one year.[54]

Contraindications

Zoledronic acid is not recommended in patients who are allergic to the active substance or to any other components of the medication. It should not be prescribed during pregnancy due to the potential damage it may cause to the fetus. Additionally, it is contraindicated in the presence of hypoparathyroidism, malabsorption syndromes and thyroid disorders. Patients with severe renal impairment (CrCl $<$ 35 ml/min) should not receive zoledronic acid as there is not enough clinical evidence for its safety in such populations. Creatinine monitoring and adequate hydration is essential in patients receiving diuretics or nephrotoxic drugs. Caution is also needed in aspirin-sensitive patients with asthma, due to reports of bronchoconstriction symptoms after the use of zoledronic acid.[54]

Drug interactions

Zoledronic acid is excreted intact in the urine and has minor or no effect on the cytochrome P450 enzyme system.[47] Aminoglycosides may decrease serum calcium levels. The simultaneous administration of zoledronic acid, therefore, may lead to severe hypocalcemia. Similarly, zoledronic acid infusion in a patient receiving loop diuretics may lead to low calcium levels. Nephrotoxic drugs, such as nonsteroidal anti-inflammatory drugs, should also be given with caution in patients receiving zoledronic acid. Finally, in the presence of renal impairment, zoledronic acid may influence the excretion of drugs primarily excreted by the kidneys, such as digoxin.[54]

Adverse events

Zoledronic acid is considered a safe and well tolerated medication when used for the treatment of postmenopausal osteoporosis. It has been mainly associated with flu-like symptoms, which usually lack severity and resolve within several days after their onset. These symptoms include fever (18.1%), myalgia (9.4%), headache (6.5%) and arthralgia (6.8%). These manifestations can be limited with the administration of acetaminophen or ibuprophen shortly after zoledronic acid infusion. The frequency of these symptoms is usually lower with subsequent infusions.[48]

Regarding the serious adverse events, no significant differences were observed between patients receiving zoledronic acid and placebo as documented in the HORIZON pivotal fracture trial with the incidence being 30.1% and 29.2% respectively.[38] All-cause mortality had an incidence of 3.4% in the zoledronic acid group and 2.9% in the placebo group. Taking into account that zoledronic acid reduces vertebral and non-vertebral fractures, which are an important cause

of disability and mortality among postmenopausal women, the use of zoledronic acid for treatment of postmenopausal osteoporosis is expected to improve survival.

Zoledronic acid has been reported to increase serum creatinine, with some rare reports of acute renal failure. On the 9th and 11th day post-dose in the HORIZON pivotal fracture trial, there was a significant increase of serum creatinine (>44 μmol/l) in the zoledronic acid group compared to placebo (1.3% and 0.4% respectively). However, 30 days post-dose, creatinine levels returned at the pre-infusion levels in more than 85% of the patients, while in the remaining patients creatinine levels had normalized by the next annual follow-up.[38,11] After 3 years no significant differences in the levels of serum creatinine or in creatinine clearance were observed between zoledronic acid group and placebo. The rare events of acute renal dysfunction in the zoledronic acid group occur mainly in patients with creatinine clearance (<31 ml/min) at baseline.[48] Similar results were observed in the HORIZON-RFT and the McClung trials.[50,52] Finally, according to Reid et al[71] no significant renal events were observed after administering different doses of zoledronic acid.

Another serious adverse event associated with zoledronic acid is atrial fibrillation (AF). In the HORIZON Pivotal Fracture Trial there was a statistically significant higher rate of serious atrial fibrillation (requiring hospitalization or becoming life-threatening) in the zoledronic acid group compared to placebo (1.3% and 0.5%, respectively).[72] However, comparing the rates of overall atrial fibrillation incidences (serious plus non serious) there was no significantly difference between the zoledronic acid and the placebo group.[38] It should be mentioned, however, that in HORIZON PFT the number of patients with arrhythmia was higher in the zoledronic acid group compared to placebo. Additionally, in most patients who developed AF the incident occurred one month after the infusion of zoledronic acid, when the drug is not detected in the circulation.

Concerning the HORIZON RFT, which included older patients, no significant difference of the serious and overall AF events was observed between zoledronic acid group and placebo.[50] The pathophysiology of zoledronic acid-associated AF remains uncertain. The electrolyte imbalances that develop after infusion, such as hypocalcemia, hypophosphatemia and hypomagnesemia could be implicated.[73,74] Up to now, healthcare practitioners are recommended to continue their prescribing as previously and patients receiving zoledronic acid to remain on their medication, as no clear association between bisphosphonates and atrial fibrillation (serious plus non-serious) could be established by FDA.[75]

Osteonecrosis of the jaw (ONJ) is another serious but rare adverse event observed during zoledronic acid treatment. ONJ is defined as the presence of exposed bone in the maxillofacial region which remains unhealed eight weeks after the diagnosis by a specialist.[76] ONJ is associated mostly with intravenous bisphosphonates compared to the oral regimens.[77] Risk factors for ONJ are head and neck radiotherapy, periodontal disease, dental surgery, edentulous regions and trauma due to poorly fitting dentures. Patients suffering from inflammatory dental disease have a seven-fold increased risk to develop ONJ. In cancer patients, predisposing factors are the underlying malignancy, chemotherapy, corticosteroids and systematic or regional infection.[78] Antiangiogenesis, impaired circulation as well as suppressed osteoclastic activity are considered as possible underlying mechanisms for this disorder.[79,80] Length of exposure in bisphosphonates is crucial for the incidence of ONJ and caution is required for treatment beyond two years.[81] According to Bamias et al[82] ONJ incidence was 1.5% among cancer patients with bone metastases treated with zoledronic acid for 12 months and 7.7% in patients treated for 37 to 48 months.

A retrospective study showed that the incidence of ONJ in cancer patients treated with bisphosphonates intravenously was 1 in 71.5. Patients who developed ONJ suffered from multiple myeloma and were receiving monthly infusions.[83] In another study, 252 cancer patients treated with bisphosphonates were evaluated prospectively for 6 years. The overall incidence of ONJ was 6.7%, while disease-specific incidence was 9.9% for myeloma, 6.5% for prostate cancer and 2.9% for breast cancer. It should be mentioned, however, that the median number of infusions was 35 in the patients who developed ONJ compared with 15 in patients without ONJ ($P < 0.001$).[82] In the Pivotal Fracture Trial, among 7.736 postmenopausal osteoporotic women, only two patients developed ONJ: one patient treated with zoledronic acid and

one patient who did not receive any therapy. ONJ resolved after appropriate treatment.[38]

Concluding, ONJ has 100-fold higher incidence in cancer patients compared to osteoporotic patients.[11] The most important risk factor for ONJ are the frequent infusions administered in cancer patients. The less frequent dosage in patients with postmenopausal osteoporosis is considered safe regarding the risk of ONJ. Guidelines concerning bisphosphonate-associated ONJ should, therefore, distinguish between osteoporosis and cancer populations. In order to minimize the risk for ONJ, a dental evaluation should be conducted before, during and after treatment.[84]

Zoledronic acid is also associated with hypocalcemia. Notable decrease in calcium levels (less than 7.5 mg/dl) occurred in 0.2% of the patients treated with zoledronic acid.[54] This electrolyte imbalance is usually asymptomatic and occurs the first days after the infusion. Symptoms may include numbness, tingling sensations, especially in the area around the mouth, muscle spasms and cramps. The hypocalcemia and the resulting secondary hyperparathyroidism can be prevented with Vitamin D and calcium administration starting 2 weeks before the infusion.[72]

Additionally, local reactions at the infusion site such as itching, redness and pain have been reported in 0.7% of patients receiving zoledronic acid intravenously.[38] Finally, 0.2% of patients treated with zoledronic acid developed ocular inflammatory events.[38] Conjunctivitis and episcleritis permits local treatment, while scleritis and uveitis require discontinuation of the treatment.[9]

Conclusions

Postmenopausal osteoporosis is a major health problem with serious social and economical aspects. Approximately 50% of women over 50 years will experience an osteoporotic fracture during their lifetime.[85] The annually administered intravenous zoledronic acid 5 mg has created an important alternative in the management of postmenopausal osteoporosis. Clinical trials, however, have shown that zoledronic acid maintains efficacy even 24 months after the infusion. The biennial administration of zoledronic acid 5 mg in patients with postmenopausal osteoporosis will improve adherence, decrease adverse events and cost, while maintaining anti-fracture efficacy.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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