Expert Opinion

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Single annual injectable treatment for postmenopausal osteoporosis

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Background: Several treatments for postmenopausal osteoporosis have become available over the last decade, but adherence to treatment is inadequate and the prevention of non-vertebral fracture by those medications is still modest. *Methods*: We have performed a literature search regarding treatment with zoledronic acid in postmenopausal women. *Results*: In the Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial, involving 7765 postmenopausal women with low bone mineral density or with prevalent vertebral fracture, women taking zoledronic acid had a 70% vertebral fracture relative risk reduction and a 41% relative risk reduction for hip fracture, at 3 years, compared to placebo. In the HORIZON Recurrent Fracture Trial, 2127 patients (76% were women) were randomized to receive either zoledronic acid or a placebo after sustaining an initial hip fracture. After a median follow-up of 1.9 years, a relative risk reduction of 35% of clinical fractures was observed. Death from all causes was reduced by 28% in the zoledronic acid group. Zoledronic acid was generally safe in those trials, although a slightly increased rate of severe atrial fibrillations was observed in the HORIZON Prevention Fracture Trial, although not in the HORIZON Recurrent Fracture Trial. The clinical significance of this remains unclear. *Conclusion*: Yearly zoledronic acid presents a new option for the treatment of postmenopausal osteoporosis, with the perspective of improving the long-term persistence of therapy because of its once-a-year regimen.

Keywords: bisphosphonates, fracture, osteoporosis, zoledronic acid

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1. Introduction

Osteoporosis, the most common bone disease, represents a substantial public health burden, with a one-in-six lifetime risk of sustaining a hip fracture in white women, which is greater than the one-in-nine lifetime risk of breast cancer [1]. More than 40% of postmenopausal women will have osteoporotic fractures of any type [2], amounting to 1.5 million fragility fractures per year for a country like the US [3]. Fractures of the vertebrae, the hip and the distal forearm are the most common, but other non-vertebral fractures including of the humerus, pelvis or ribs are also of clinical importance. Mortality is increased in women with hip fractures, who die 10 – 20% more than expected for their age within the first year [4] and this excess mortality persists for several years after hip fracture [5]. Raised mortality is also observed in women with vertebral fractures [6]. Loss of independence and entry into nursing homes are also common consequences of hip fractures [7].

Risk factors for fractures include age, familial and personal history of fracture, low body mass index, smoking, rheumatoid arthritis, prior use of

corticosteroids and decreased bone mineral density (BMD) [8,9]. In postmenopausal women, oestrogen deficiency increases bone remodelling, with more resorbed bone than newly formed bone as a result, thus accelerating bone loss and causing trabecular thinning and disconnection, cortical thinning and porosity [10].

Various therapies for osteoporosis have been introduced in the last 10 years. As it has been recently proposed, these medications may be classified generally as anabolic drugs and anticatabolic drugs [11]. Some compounds, such as calcium, vitamin D and strontium ranelate, however, do not fall into those broad categories. The first medications to prove their antifracture efficacy were anticatabolic (or antiresorptive) agents. Their main characteristic is to reduce bone turnover, with various degrees of potency. The weak anticatabolic agents are nasal spray calcitonin and raloxifene. They exhibit only small increases in BMD, and reduce biochemical markers of bone turnover of 20 – 30%. Raloxifene can reduce vertebral fracture risk by 30% among women with prevalent vertebral fracture [12], and this reduction rises to 50% in those with low bone mass but no history of vertebral fracture. Nasal calcitonin might also reduce vertebral fracture risk [13] but this remains controversial because of methodological issues in the PROOF trial [14]. There is no evidence for the efficacy against non-vertebral fractures with those two drugs. More potent anticatabolic agents, such as bisphosphonates, can halve vertebral facture risk [15-20]. Their efficacy on non-vertebral fractures has also been established [21], but it is of smaller magnitude than that observed with vertebral fracture. At present, the only widely available anabolic drug is teriparatide, which is a recombinant 1 – 34 parathyroid hormone peptide, administered by daily subcutaneous injections for 18 months. This drug increases bone turnover, with a greater increase in bone formation than in bone resorption. Its efficacy on preventing vertebral and non-vertebral fracture in postmenopausal women with severe osteoporosis has been established in one randomized placebo-controlled trial. Vertebral fractures were reduced by two-thirds and non-vertebral fractures by half [22]. Intact PTH is also available in some European countries. This compound has been shown to reduce vertebral fracture risk only in a group of postmenopausal women with osteoporosis of moderate severity [23]. The effectiveness of calcium and vitamin D supplements has been established in several trials, in patients with deficiency [24]. Strontium is a bone-seeking trace element which can decrease bone resorption and increase bone formation, without affecting bone mineralization. In the SOTI trial, the incidence of new vertebral fractures was reduced by 41% after 3 years of treatment of 1649 postmenopausal osteoporotic women with 2 g/day of strontium ranelate [25]. In the TROPOS trial, which enrolled 5091 women (mean age 76), non-vertebral fractures were reduced by 16%, and vertebral fractures by 39% [26] with this compound. Strontium ranelate has now been marketed in various European countries for the treatment of postmenopausal osteoporosis.

Although those drugs have transformed the management of postmenopausal osteoporosis, there are still unmet needs for the reduction of the non-vertebral fracture risk, especially hip fracture, which remains modest with current medications. In addition, drug compliance is generally not satisfactory, with inadequate benefit from current drugs as a result.

2. Rationale for intermittent treatment of osteoporosis

Persistence with antiosteoporosis drugs is poor, as with most chronic diseases [27,28]. Thus, in a cohort of older American women, drug persistence was only 45% one year after starting a treatment for osteoporosis [29]. In another analysis performed in California, only 25% of women were still taking their medication at one year [30]. In another study conducted in North America, raloxifene and bisphosphonates were frequently stopped and the main reason for treatment interruption was the occurrence of adverse events [31]. Antifracture benefit, however, improves as much as compliance increases [32].

One of the limitations of oral bisphosphonates use was its daily dosage. Weekly regimens have been developed to diminish the treatment annoyance. In a recent analysis, 46% of women on a weekly formulation were still taking their drug at one year, whereas only 33% of those on a daily dosage were still on medication [33]. More recently, a monthly dosage of ibandronate has been marketed, with the goal of enhancing persistence [34,35]. Another limitation of oral bisphosphonates is the possibility of digestive adverse events such as abdominal pain, dyspepsia and, rarely, oesophagitis.

3. Methods

We have performed a literature search in PubMed, using the following terms: zoledronic acid, postmenopausal osteoporosis, bisphosphonates. We have selected articles relevant to the treatment of postmenopausal osteoporosis with zoledronic acid. We have also used articles on zoledronic acid that we were aware of.

4. Pharmacology of zoledronic acid

Zoledronic acid is a potent nitrogen-containing BP, used for the treatment of Paget's disease of the bone, hypercalcemia, multiple myeloma, androgen-deficiency-induced bone loss in prostate cancer patients, prostate cancer bone metastases and osteolytic bone metastases. Its value in the treatment of postmenopausal osteoporosis has also been evaluated more recently.

It has been found in rat models that zoledronic acid produces dose-dependent increases in cancellous bone

volume and connectivity, 100 times more effectively than pamidronate, and decreases bone resorption, if given as subcutaneous injections for 10 days [36].

In a study involving 40 ovariectomized adult rhesus monkey – an animal model of postmenopausal bone loss – the animals were randomly assigned to one control group and four ovariectomy groups. The control and one ovariectomy group received saline, and the three other ovariectomy groups were given 0.5, 2.5 or 12.5 µg/kg zoledronic acid by a single weekly subcutaneous injection, for 69 weeks [37]. Spine, total body and radius BMD were either preserved or increased by zoledronate, dose-dependently, up to week 39, and stabilized thereafter. Simultaneously, biochemical markers of bone turnover significantly decreased in monkeys receiving zoledronic acid, proportionally to the dosage, and remained reduced until the end of the study, compared with animals on the placebo. Thus, zoledronic acid appears to be a potential therapy for postmenopausal bone loss.

In a Phase II, randomized, double-blind, placebo-controlled trial, zoledronic acid or placebo were given intravenously to 351 postmenopausal women with low BMD (T score < -2), for one year. These patients received placebo or intravenous zoledronic acid at doses of 0.25, 0.5 or 1.0 mg every 3 months, or 2.0 mg every 6 months, or a single annual 4.0 mg dose [38]. All women received a 1 g/day calcium supplement.

All zoledronic acid regimens produced similar increases in lumbar spine and femoral neck BMD, spanning 4.3 – 5.1% at the spine, compared to stable BMD in the placebo group. Biochemical markers of bone resorption (urinary N-terminal telopeptide of type I collagen [NTX], serum C-terminal telopeptide of type I collagen [CTX]) were rapidly and consistently suppressed during the trial, while markers of bone formation were also diminished, albeit later after beginning treatment. Myalgia and transient fever were the most common adverse events. Those effects on surrogate markers were as great as those observed with bisphosphonates with proven efficacy to reduce osteoporotic fracture risk.

After completion of this Phase II study, two consecutive, open-label extensions have been conducted, over 5 years [39]. In the first extension, most patients received 4 mg once a year. They entered the second extension thereafter and received either zoledronic acid 4 mg/year or calcium alone. Patients were analyzed according to the duration of their treatment with zoledronic acid (2, 3, or 5 years). All groups exhibited substantial increases in BMD and significant reduction in biochemical markers of bone turnover. A third of patients, however, did not have an optimal reduction in bone-specific alkaline phosphatase, even after repeated zoledronic acid infusions. This frequent suboptimal response was not observed when examining results of serum CTX-1 measurements. Taken together, these results may suggest that a 4 mg yearly infusion may not have been adequate for all the postmenopausal patients.

In a randomized, double-blind, double-dummy trial that compared the onset of action of zoledronic acid 5 mg and alendronate 70 mg in postmenopausal women with low bone mineral density [40], the reduction in markers of bone resorption was significantly greater at week one in women on zoledronic acid than in those on alendronate. The difference between the two drugs diminished over time, but a slight difference in favor of zoledronic acid remained after 12 weeks.

The 1-year Phase II trial [38] has paved the way for conducting a large Phase III trial program (the HORIZON trials) designed to demonstrate the ability of zoledronic acid 5 mg given intravenously once a year to reduce osteoporotic fracture risk.

5. Clinical results with zoledronic acid in the treatment of postmenopausal osteoporosis

So far, the results of two large Phase III multicenter randomized placebo-controlled trials have been published. The HORIZON Pivotal Fracture Trial was conducted among postmenopausal osteoporotic women with and without prevalent fracture [41]. The HORIZON Recurrent Fracture Trial was performed to test the ability of the compound to reduce fracture risk among men and women with recent hip fractures [42].

6. The HORIZON Pivotal Fracture Trial

The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial was an international, multicenter, randomized, double-blind, placebo-controlled trial involving postmenopausal women with osteoporosis. Patients were randomly assigned to receive either a 15-min intravenous administration of zoledronic acid (5 mg) or placebo at baseline (day 0), at 12 months, and at 24 months. In addition, all patients received oral daily calcium (1000 – 1500 mg) and vitamin D (400 – 1200 IU). Patients were monitored for 3 years to measure the incidence of new vertebral and non-vertebral fracture.

Postmenopausal women between the ages of 65 and 89 years could be enrolled if they had a bone mineral density T-score of -2.5 or less at the femoral neck, with or without prevalent vertebral fracture, or a T-score of -1.5 or less, with radiological evidence of at least two mild vertebral fractures or one moderate vertebral fracture. Previous use of oral bisphosphonates was allowed, with the duration of the washout period dependent on the duration of previous use. Concomitant use of several antiosteoporosis drugs was permitted, such as raloxifene, calcitonin, tibolone, tamoxifen, dehydroepiandrosterone, ipriflavone and medroxyprogesterone. Patients were stratified according to their baseline osteoporosis therapy: those in stratum 1 did not take any bone medication at baseline, whereas those

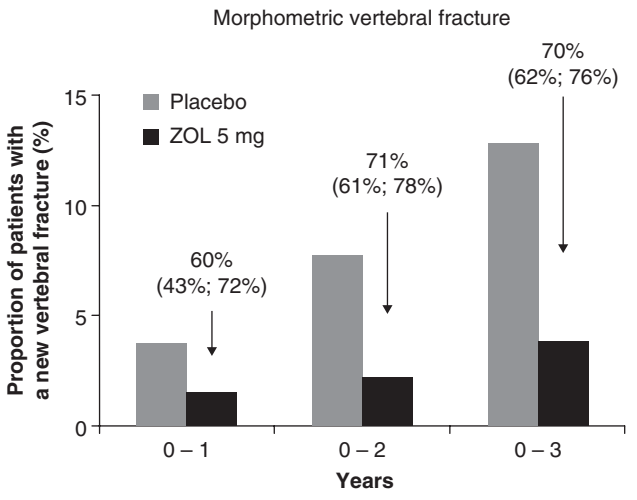

Figure 1. Vertebral fracture risk reduction with zoledronic acid compared with placebo among postmenopausal osteoporotic women from the HORIZON Prevention Fracture Trial.

in stratum 2 were on an antiosteoporosis drug when they started the trial.

There were two main outcomes in this trial: the incidence of new vertebral fracture in stratum 1 and the incidence of hip fracture in both strata. Secondary efficacy end points included any non-vertebral fracture, any clinical fracture and clinical vertebral fracture. Other secondary end points were changes in bone mineral density at the total hip, femoral neck and lumbar spine and changes in markers of bone resorption (serum C-telopeptide of type I collagen, CTX) and formation (bone-specific alkaline phosphatase, BSAP and N-terminal propeptide of type I collagen, PINP).

A total of 7765 women were randomized to receive either zoledronic acid (n = 3889) or placebo (n = 3876). Their mean age was 73 years, 63% had prevalent vertebral fracture and 79% had no other osteoporosis medication at baseline (stratum 1). Eighty-four percent of patients remained on follow-up at 3 years. Women taking zoledronic acid had a 70% vertebral fracture relative risk reduction at 3 years (**Figure 1**). Fracture risk reduction after 1 and 2 years of treatment was comparable to that observed after 3 years (**Figure 1**). The relative risk reduction for hip fractures was 41% with zoledronic acid (**Figure 2**). Non-vertebral fractures were reduced by 25%, all clinical fractures by 33% and clinical vertebral by 77%, in women on zoledronic acid. Height loss was also slowed in the active treatment group compared to placebo (-4.2 mm vs -7.0 mm, $p < 0.001$).

Surrogate variables such as the variation in BMD and biochemical markers of bone turnover were also positively affected by the treatment with zoledronic acid. Bone mineral density at the hip increased by 6% and by 6.7% at the spine after 3 years of follow-up, compared with the placebo. All three markers of bone turnover (serum CTX, BSAP and PINP) decreased significantly compared with the placebo group, when they were measured 12 months after starting therapy. At 6 and 12 months after each infusion, there was no further decline in these concentrations (**Figure 3**).

The numbers of patients who died, had a serious adverse event, or discontinued follow-up because of an adverse event did not significantly differ between the study groups. Among patients on zoledronic acid, 31.6% had a brief flu-like syndrome after the first infusion, compared with 6.2% in the placebo group. Nine to eleven days after the infusion, 1.3% of patients on zoledronic acid and 0.5% of patients in the placebo group had a transient increase of more than 0.5 mg/dl in serum creatinine levels. The number of patients who had arrhythmia in the zoledronic acid group (266 patients, or 6.9%) was significantly higher than that in the placebo group (203 patients, or 5.3%; $p = 0.003$). Serious atrial fibrillation, a subcategory of all arrhythmias, was more common among patients in the zoledronic acid group. In the zoledronic acid group, 50 patients had serious atrial fibrillation (1.3%), as compared with 20 patients (0.5%) in the placebo group. Among the patients in the zoledronic acid group, 47 out of 50 serious atrial fibrillation events occurred more than 30 days after the infusion. The occurrence of stroke, or death from stroke, did not differ between the two groups. Two cases of potential osteonecrosis of the jaw were identified (one in the placebo group and one in the zoledronic acid group).

In a substudy of the HORIZON fracture trial, 152 patients underwent bone biopsy. Zoledronic acid reduced bone turnover by a median 63% and preserved bone structure and volume, with evidence of ongoing bone remodeling in 99% of biopsies obtained [43]. Bone formation was normal and there was no evidence of mineralization defects. Concomitant administration of other antiosteoporosis drugs did not affect the tissue-level response to zoledronic acid. Analysis of bone structure by microCT revealed higher trabecular bone volume (BV/TV) in the zoledronic acid group (median, 16.6 vs 12.8%, $p = 0.020$). In addition, five of 33 patients treated with zoledronic acid exhibited higher trabecular numbers ($p = 0.008$), decreased trabecular separation ($p = 0.011$) and a trend toward improvement in connectivity density ($p = 0.062$), all indicating better preservation of trabecular structure after treatment with zoledronic acid.

7. The HORIZON Recurrent Fracture Trial

The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Recurrent Fracture Trial was an international, multicenter, randomized, placebo-controlled trial involving men and women with recent hip fracture [42]. Patients were randomized to receive

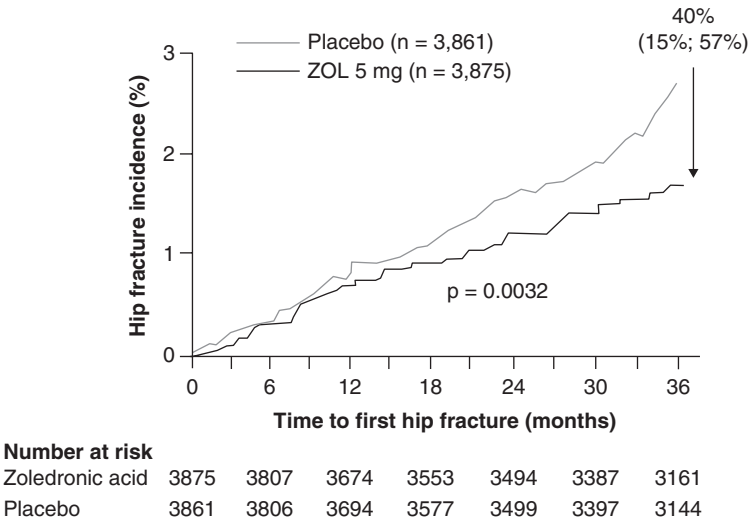

Figure 2. Hip fracture risk reduction with zoledronic acid compared with placebo among postmenopausal osteoporotic women from the HORIZON Prevention Fracture Trial.

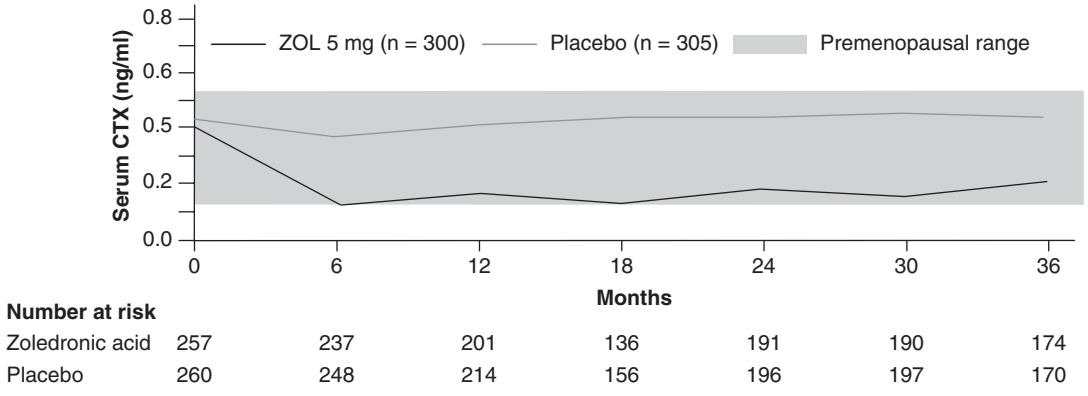

Figure 3. Variation in serum CTX after zoledronic acid infusions, in comparison with the normal (premenopausal) range.

a yearly infusion of either 5 mg of zoledronic acid or a similar infusion of placebo. The treatment was administered within 90 days of the surgical repair of the hip fracture, and once a year thereafter. All patients were supplemented with calcium and vitamin D. All those patients were unable or unwilling to take an oral bisphosphonate. A parallel therapy with calcitonin, a SERM, tibolone and hip protectors was authorized.

The primary end point was a new clinical fracture. Secondary end points included the change in bone mineral density at the non-fractured hip, and new vertebral and non-vertebral fracture, as well as second hip fractures and death. Among 2127 patients, 76% were women, 1065 received zoledronic acid and 1062 were on placebo.

After a median follow-up of 1.9 years, the observed fracture rate of clinical fracture was 8.6% in the zoledronic acid group and 13.9% in the placebo group, representing an absolute risk reduction of 5.3% and a relative risk reduction of 35%. There was also a non-significant 30% second hip fracture relative risk reduction associated with use of zoledronic acid. Death from all causes was reduced by 28% in the zoledronic acid group (**Figure** 4). Bone mineral density at the total hip increased in the zoledronic acid group by 2.6% at 12 months, 4.7% at 24 months and 5.5% at 36 months and declined in the placebo group by 1.0, 0.7 and 0.9%, respectively.

The incidence of pyrexia, myalgia and bone pain was increased among patients who received zoledronic acid,

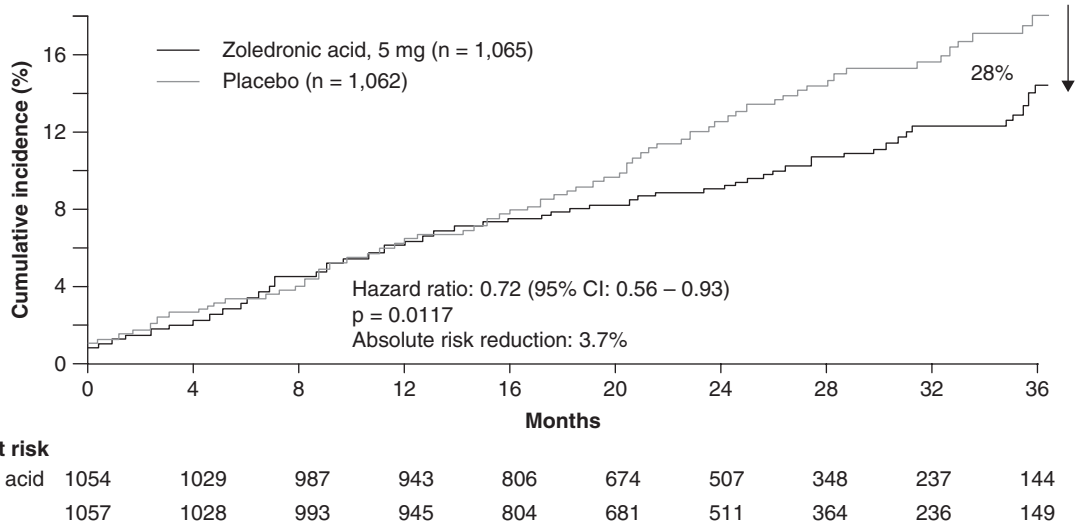

Figure 4. Reduction of mortality from all causes associated with the use of zoledronic acid.
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whereas the incidence of serious adverse events was comparable in the groups. Similarly, there was no difference for the occurrence of serious renal adverse events, arrhythmia and atrial fibrillation. No case of osteonecrosis of the jaw was reported.

8. Yearly zoledronic acid: in practice

Zoledronic acid has been marketed recently in North America (Reclast®) and is about to be launched in various European countries (Aclasta®). Zoledronic acid (5 mg) is infused once a year, intravenously, over at least 15 mn, with 100 ml of saline. A calcium and vitamin D supplement is recommended. The calcium dose varies from 1000 to 1500 mg/d, depending on food calcium intake, and the vitamin D intake ranges between 400 and 1200 IU, according to the patients' vitamin D sufficiency status. In elderly patients with low levels of vitamin D (below 45 nmol/l), a loading dose of vitamin D appears to be necessary to avoid hypocalcemia. In the HORIZON Recurrent Fracture Trial, this loading dose ranged from 50,000 to 125,000 IU of vitamin D2 or D3.

No dose adjustment is necessary among elderly patients, but the use of zoledronic acid is not recommended in those with a creatinine clearance below 30 ml/mn because it has not been evaluated in this kind of population. There is no drug interaction study specific to zoledronic acid available. Caution should be applied in patients who simultaneously receive medications that may reduce renal function, including aminoglycosides and diuretics.

9. Conclusion

Yearly intravenous zoledronic acid 5 mg is an effective treatment to reduce the incidence of both vertebral and non-vertebral fracture among postmenopausal osteoporotic women. This treatment has been well tolerated in clinical trials. This intermittent regimen is likely to improve convenience for patients and persistence on the therapy as a result.

10. Expert opinion

The validity of results from clinical trials is critical for clinical practice and for the healthcare systems which reimburse the drugs. Patient retention must be high so the intention to treat analysis remains reliable, along with sound randomization and statistical analysis. A large spectrum of the disease must be enrolled to allow for good generalizability of trial results. The HORIZON trials have shown such qualities. In the HORIZON Pivotal Fracture trial [41], 84% of patients remained in active follow-up and 81% received all three infusions. For comparison with other major Phase III osteoporosis trials, 88% of patients were still taking the drug after three years in the FIT I trial testing alendronate [16], complete follow-up data at 3 years were available for only 64% of the women in the HIP trial examining risedronate [44], or 64 – 68% (according to different treatment groups) completed the study in the 3-year BONE trial testing the efficacy of oral ibandronate [34]. In the HORIZON Recurrent Fracture Trial [42], which was an event-driven trial, 71% of the patients completed the trial but only 3% were lost to follow-up. Results from the HORIZON program apply to a wide range of severity of postmenopausal osteoporosis. Indeed, women could have osteoporosis with or without prevalent vertebral fracture, with ages ranging from 65 to 89. They could have already received certain osteoporosis medications, and there were few exclusion criteria. Patients in the HORIZON Recurrent

Fracture Trial had had a recent hip fracture. Thus, a wide spectrum of postmenopausal women with osteoporosis has been enrolled in those trials, ranging from mild osteoporosis to severe osteoporosis with several vertebral fractures or a first hip fracture, providing excellent generalizability of results.

So far, treatment of osteoporosis after a first hip fracture has often been recommended because the incidence of the second hip fracture is significant [45], but there has been no clinical trial proving the effectiveness of treatments in this particularly frail population. The HORIZON Recurrent Fracture Trial is the first trial to demonstrate a significant reduction in the risk of new fractures in patients with a recent first hip fracture using yearly 5 mg zoledronic acid started shortly after the fracture. These data should form the basis to establish a new standard of treatment in this elderly population. Specific programs linking physicians taking care of osteoporotic patients (primary care physicians, rheumatologists, endocrinologists, geriatricians) to orthopedic surgeons would be valuable to expand the secondary prevention of fracture in the elderly with recent hip fracture, which is currently close to nil.

In the HORIZON Pivotal Fracture Trial, 2.3% of women had hypocalcemia, defined as serum calcium below 2.075 mmol/l, 9 – 11 days after the infusion. Those episodes were transient and asymptomatic in all cases. In the HORIZON Recurrent Fracture Trial, although the patients were older and more frail, fewer episodes of hypocalcemia were observed (0.3%). This may be due to the loading dose of vitamin D patients received before their first zoledronic acid infusion. Therefore, hypocalcemia appears to be a rare and subclinical event in women receiving zoledronic acid. In older patients, however, it is probably wise to measure serum dihydroxy-vitamin D and to give an adequate vitamin D supplement, including a loading dose if judged necessary, to avoid hypocalcemia as much as possible.

In the HORIZON Pivotal Fracture Trial, but not in the HORIZON Recurrent Fracture Trial, serious atrial fibrillation occurred more frequently in the zoledronic acid group (1.3%) than in the placebo group (0.5%, $p < 0.001$). This finding has prompted several groups to report data on atrial fibrillation from other bisphosphonates trials. In the FIT trials, a trend was observed for the occurrence of serious atrial fibrillation, with a relative hazard of 1.51 (0.97, 2.40) [46]. In the Phase III trials of risedronate for osteoporosis, there was no difference in the incidence of atrial fibrillation, stroke, or death related to cardiovascular disease between the placebo and treated groups [47]. In a population-based case control study in Denmark based on medical databases, involving 13,694 patient with atrial fibrillation/flutter and 68,470 controls, there was no association between use of oral bisphosphonate and the risk of atrial fibrillation/flutter [48]. In this context of conflicting data on the influence of bisphosphonates on the risk of atrial fibrillation, it remains possible that the observation of increased risk in the HORIZON Pivotal Fracture Trial is a chance finding induced by multiple comparisons. The possibility that this arrhythmia might be related to subclinical hypocalcemia and the resulting secondary hyperparathyroidism [49], however, points to the need for monitoring this potential cardiovascular event when zoledronic is marketed worldwide.

One of the concerns with new antiresorptive agents is their bone safety, regarding the risk of mineralization defects and the risk of over-suppression of bone turnover. In the ancillary bone biopsy study of the HORIZON trial, there was no mineralization defect [43]. Bone turnover was diminished by the same magnitude that is observed with alendronate. All 152 biopsies but one showed evidence of tetracycline label, indicating preserved remodeling capacity. One year after treatment, before the next infusion, an increase in serum markers of bone resorption was visible, consistent with this preservation of bone remodeling capacity. It is likely that zoledronic acid may be started among patients who have already received other bisphosphonates. In a randomized double-blind double-dummy trial, conducted in postmenopausal women with low BMD who had been previously treated with alendronate for an average of 4 years, patients received either yearly zoledronic acid 5 mg or oral weekly alendronate 70 mg over 1 year [50]. Bone mineral density was maintained in both groups, with no significant difference in BMD change between the two groups. In addition, zoledronic acid further diminished markers of bone resorption, which increased thereafter, suggesting a preserved bone remodeling capacity. Thus, there is ample evidence for satisfactory bone safety with the use of yearly zoledronic acid over 3 years.

Osteonecrosis of the jaw associated with the use of bisphosphonates has been described since 2003. It is defined by exposed bone in the maxillofacial region during at least 8 weeks in patients previously or currently taking bisphosphonates, who did not receive radiotherapy of the maxillofacial region [51]. The incidence of osteonecrosis of the jaw among patients receiving monthly infusions of pamidronate or zoledronic acid to treat malignancy ranges between 1 and 10%. In patients taking bisphosphonates for the treatment of Paget's disease of bone or osteoporosis, it seems to be an exceptional event, with an incidence of 1/100,000 per patients, per year. In the HORIZON Pivotal Fracture Trial, there was one case in the placebo group and one case in the zoledronic acid group. No case of osteonecrosis of the jaw was identified in the HORIZON Recurrent Fracture Trial. Previous studies have shown that the incidence of osteonecrosis of the jaw is proportional to the cumulative dose of bisphosphonate, explaining the much higher incidence among patients with malignancies than those with osteoporosis. It is likely that the incidence of osteonecrosis of the jaw that might be observed in patients receiving zoledronic acid is comparable to that encountered with previous oral bisphosphonates used for osteoporosis. Therefore, at this stage, it has been recommended by the

American Society for Bone and Mineral Research Task Force [51] that patients be informed about the risk of osteonecrosis of the jaw, maintain good oral hygiene and have regular dental visits. There is no contraindication to dental implant placement. Current evidence supports applying the same recommendations for annual zoledronic acid as for older oral bisphosphonate therapies.

Many patients on long-term oral bisphosphonates stop their therapy within the first year. Therefore, all options that may improve long-term persistence are valuable. Two studies have shown that most patients who had taken both alendronate and zoledronic acid preferred zoledronic acid [40,50]. It is likely that a yearly regimen – preferred by patients – will improve persistence of postmenopausal osteoporosis treatments.

Declaration of interest

RD Chapurlat has received research funding and/or speaker and consulting honoraria from Merck Sharp & Dohme, Procter and Gamble, sanofi-aventis, Novartis, Roche, Servier and Eli Lilly.

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