



ROLE OF A ONCE-YEARLY INTRAVENOUS ZOLEDRONIC ACID 5 POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS

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ABSTRACT

OBJECTIVES: To determine the efficacy of mg in reducing risk of once-yearly intravenous zoledronic acid (ZOL) 5 clinical vertebral, nonvertebral, and any clinical fractures in elderly osteoporotic postmenopausal women.

DESIGN: A post hoc subgroup analysis of pooled data from the Health Outcome and Reduced Incidence with Zoledronic Acid One Yearly (HORIZON) Pivotal Fracture Trial and the HORIZON Recurrent Fracture Trial.

SETTING: Multicenter, randomized, double-blind, placebo-controlled trials.

PARTICIPANTS: Postmenopausal women (aged ≥ 75) with documented osteoporosis (T -score ≤ -2.5 at femoral neck or ≥ 1 prevalent vertebral or hip fracture) or a recent hip fracture.

INTERVENTION: Patients were randomized to receive mg ($n=1,961$) or placebo ($n=1,926$) at an intravenous infusion of ZOL 5 baseline and 12 and 24 months.

MEASUREMENTS: Primary endpoints were incidence of clinical vertebral and nonvertebral and any clinical fracture after treatment.

RESULTS: At 3 years, incidence of any clinical, clinical vertebral, and nonvertebral fracture were significantly lower in the ZOL group than in the placebo group (10.8% vs 16.6%, 1.1% vs 3.7%, and 9.9% vs 13.7%, respectively) (hazard ratio (HR)=0.65, 95% confidence interval (CI)=0.54–0.78, $P<.001$; HR=0.34, 95% CI=0.21–0.55, $P<.001$; and HR=0.73, 95% CI=0.60–0.90, $P=.002$, respectively). The incidence of hip fracture was lower with ZOL but did not reach statistical significance. The incidence rate of postdose adverse events were higher with ZOL, although the rate of serious adverse events and deaths was comparable between the two groups.

CONCLUSION: mg was Once-yearly intravenous ZOL 5 associated with a significant reduction in the risk of new clinical fractures (vertebral and nonvertebral) in elderly postmenopausal women with osteoporosis.

Keywords: pain , osteoporosis , zoledronic , post menopausal

INTRODUCTION

Osteoporosis is common in elderly postmenopausal women and is associated with a high incidence of fractures. The incidence of osteoporotic fractures is reported to increase with age,¹ and more than 50% of all fragility fractures in the community arise in women aged 75 and older.²

Vertebral and hip fractures are highly prevalent in older adults^{2,3} and contribute to significant morbidity and mortality in this age group.⁴⁻⁹ The incidence of vertebral fractures in women increases strongly with age, ranging from 7.8 per 1,000 person-years at age 55 to 65 to 19.6 per 1,000 person-years at age 75 and older.¹⁰

Moreover, patients with previous fractures have higher risk of future fractures^{11,12} as they lose significant bone and muscle mass.¹³ Hip fracture is a strong risk factor for subsequent nonhip skeletal fractures in the elderly population. It is not only a marker of prevalent osteoporosis but also a precipitant of functional and bone density decline, which further increases fall and fracture risk.¹⁴

Several studies have shown a significant relationship between increasing age and decreasing likelihood of receiving effective osteoporosis treatment.¹⁴⁻¹⁸ Thus, untreated osteoporosis leads to an increase in hospitalization and medical expenditure.¹⁹ This therapeutic challenge is mainly attributed to two issues. First, elderly patients have been underrepresented in osteoporosis clinical trials, and the efficacy and safety of the available drugs for this population remains unclear.²⁰ Second, the complex and frequent administration requirements of oral bisphosphonates makes it more challenging in patients with cognitive or functional impairments and in those who take multiple oral medications. Consequently, the compliance with oral bisphosphonates is low, and therefore, this disease remains undertreated.²¹⁻²⁴

A once-yearly intravenous infusion of zoledronic acid (ZOL) mg is a more-attractive therapeutic option in the management of 5 osteoporosis than daily, weekly, or even monthly regimens of oral bisphosphonates.²⁵ mg in preventing bone loss and Moreover, the use of intravenous ZOL 5 reducing the risk of fractures is well established in postmenopausal osteoporosis.²⁵⁻²⁸ ZOL is the first intravenous therapeutic agent with documented protection against vertebral and nonvertebral fractures, including hip fracture,²⁵⁻²⁸ but the efficacy and safety of intravenous bisphosphonates in postmenopausal women aged 75 and older is not well established.

Given the high prevalence of osteoporosis, the underuse of antiresorptive treatment, and the paucity of efficacy and safety data regarding bisphosphonate therapy for osteoporosis in elderly postmenopausal women, a post hoc analysis was conducted to determine the mg in reducing the efficacy and safety of once-yearly intravenous ZOL 5 risk of vertebral and nonvertebral fractures in elderly postmenopausal women aged 75 and older with osteoporosis.

METHOD

This post hoc analysis presents the results of pooled data from Health Outcome and Reduced Incidence with Zoledronic Acid One Yearly (HORIZON) Pivotal Fracture Trial²⁵ and the HORIZON Recurrent Fracture Trial.²⁸ Both studies were multicenter, randomized, double-blind, placebo-controlled trials.

The HORIZON Pivotal Fracture Trial included 7,765 postmenopausal women with documented osteoporosis (i.e., femoral neck BMD T -score ≤ -2.5 with or without evidence of existing vertebral fracture or a femoral neck BMD T -score ≤ -1.5 with radiological evidence of at least two mild vertebral fractures or one moderate vertebral fracture). The HORIZON Recurrent Fracture Trial included 2,127 patients (men and women) within 90 days of surgical repair of low-trauma hip fracture. In both studies, patients were randomized to receive a once-yearly 15-minute intravenous infusion mg or placebo (on Day 0 and at 12 and 24 months) and were of ZOL 5 monitored over a period of 3 years. In the HORIZON Pivotal Fracture Trial, patients were allowed to take concomitant therapy for osteoporosis (raloxifene, calcitonin, tibolone, and hormone replacement therapy) at baseline and during the follow-up. Conversely, in the HORIZON Recurrent Fracture Trial, patients continued to take concomitant medications at the investigator's discretion. Previous use of other bisphosphonates or parathyroid hormone was allowed with a washout period according to the drug and duration of usage. Previous use of strontium or sodium fluoride was not allowed. In the

HORIZON Pivotal Fracture Trial, patients were stratified into Stratum I (patients not taking any osteoporosis medications but taking calcium and vitamin D at the time of randomization) or Stratum II (patients who were taking an allowed medication such as hormone therapy, raloxifene, calcitonin, or tibolone along with calcium and vitamin D at the time of randomization). Patients with hypersensitivity to bisphosphonates, creatinine clearance less mL/min, and corrected serum calcium level greater than 2.8 or less than 2.0

In addition to the study drug, all patients received IU). Patients in the mg) and vitamin D (400–1,200 calcium (1,000–1,500 HORIZON Recurrent Fracture Trial were given a loading dose of vitamin D₂ U) or vitamin D (75,000–125,000₃ U) 14 days before infusion of the study drug, depending upon their levels of serum 24-hydroxy vitamin D. (50,000–75,000

The primary endpoints in the HORIZON Pivotal Fracture Trial were new morphometric vertebral (in Stratum I) and hip (in both strata) fractures. The secondary efficacy endpoints were new clinical, clinical vertebral, and nonvertebral fractures and changes in bone mineral density (BMD) at the total hip, femoral neck, and lumbar spine along with bone turnover markers level. The primary endpoint in the HORIZON Recurrent Fracture Trial was a new clinical fracture (morphometric vertebral fractures were not assessed) excluding facial and digital fractures. The secondary efficacy endpoints were new clinical vertebral, nonvertebral, and hip fractures and changes in total hip and femoral neck BMD. Both HORIZON trials were conducted in accordance with the Declaration of Helsinki and were approved by the appropriate local ethics committees and institutional review boards.

The primary efficacy variables were the cumulative incidence of clinical vertebral and nonvertebral fractures or any clinical fracture over 3 years in patients aged 75 and older. Morphometric vertebral fracture incidence was not assessed in the HORIZON Recurrent Fracture Trial; therefore, the focus of this analysis was on the incidence of clinical fractures, nonvertebral fractures, and clinical vertebral fractures. The secondary efficacy variables were the incidence of hip fractures, changes in BMD at the femoral neck, and total hip BMD at 1 and 3 years.

In the HORIZON Pivotal Fracture Trial, a central reader blinded to the study group assignment compared the community-obtained radiograph for a clinical vertebral fracture with the baseline study radiograph. A central committee assessed and confirmed the radiological or surgical report for nonvertebral fractures and excluded the fractures related to excessive trauma.

In the HORIZON Recurrent Fracture Trial, clinical vertebral fracture was defined as new or worsening back pain with a reduction in vertebral height of 20% (Grade 1) or more from the baseline radiograph or a reduction in the vertebral body height of 25% (Grade 2) or more if no baseline radiograph was available. A nonvertebral fracture, confirmed according to a radiograph or medical document, was defined as a skeletal fracture that was not a vertebral, facial, digital, or skull fracture. The details of the methods of assessment have been described elsewhere.^{25,28}

Total hip BMD was derived from the femoral neck, trochanter, and intertrochanter BMD measurements performed using dual X-ray absorptiometry (Hologic, Bedford, MA, or GE Lunar, Madison, WI, dual-energy X-ray absorptiometry machines). All BMD measurements were corrected for any site- and equipment-related differences.^{29,30} Changes in bone turnover markers (BTMs; serum β -C-telopeptide (β -CTx), bone-specific alkaline phosphatase (BSAP), and N-terminal propeptide of type I collagen (P1NP) from baseline were assessed in the HORIZON Pivotal Fracture Trial alone.

RESULTS

There were 9,354 postmenopausal women included in both HORIZON trials: 5,467 younger than 75 and 3,887 aged 75 and older. Femoral neck BMD was similar in both age groups (femoral neck *T*-score ≤ -2.5 : 64.4% of those <75 , 70.0% of those ≥ 75).

The incidence of any clinical fracture, clinical vertebral, or nonvertebral fracture in postmenopausal women aged 75 and older was significantly lower in the ZOL group than in the placebo group over 3 years ($P < .001$, $P < .001$, and $P = .002$, respectively). A similar finding has been shown for any clinical fracture and clinical vertebral fractures at 1 year ($P = .03$ and $P = .009$, respectively), but the incidence of nonvertebral fracture at 1 year and hip fracture at 1 and 3 years was lower for the ZOL group although not significantly so.

The benefit observed in relative risk reduction of clinical fractures, clinical vertebral fractures, and nonvertebral fractures was comparable in patients younger than 75 and aged 75 and older 1 and 3 years after treatment, and the treatment-by-age group interactions were not statistically significant. However, patients younger than 75 showed a significant benefit in hip fracture risk reduction at 3 years ($P<.001$) that was not observed in those aged 75 and older, and this treatment-by-age group interaction was statistically significant between the two age groups ($P=.04$) because of the greater reduction in hip fracture incidence in patients younger than 75. In patients aged 75 and older, femoral neck and total hip BMD was significantly greater in those treated with ZOL than in patients receiving placebo (all $P<.001$). This was comparable in the ZOL-treated patients younger than 75, and the treatment-by-age group interactions were not statistically significant.

BTMs (serum β -CTX, BSAP, and P1NP) were measured in the HORIZON Pivotal Fracture Trial only and were significantly lower in ZOL- than placebo-treated patients in both age groups (all $P<.001$); the absolute levels were similar across the age groups.

The incidence of AEs within 3 days of study drug infusion was higher with ZOL than in the placebo group in both age groups during the 3-year study period. In addition, postdose symptoms occurring within 3 days of the study drug infusion were significantly higher with ZOL in patients aged 75 and older (41.5% vs 25.7%, $P<.001$) and in patients younger than 75 (51.8% vs 24.9%, $P<.001$). Incidence rates of renal events, including increase in serum creatinine and creatinine clearance; deaths; and SAEs were similar in the two treatment arms for both age groups.

DISCUSSION

In the post hoc analysis presented, once-yearly intravenous ZOL 5 mg treatment over 3 years significantly reduced the risk of any clinical, clinical vertebral, and nonvertebral fracture in elderly postmenopausal women aged 75 and older with documented osteoporosis or a recent hip fracture. These findings provide evidence of the efficacy of this dosing regimen in patients aged 75 and older reported in this analysis. Moreover, the current analysis showed that the efficacy was comparable in both age groups (≥ 75 and < 75).

The data in patients aged 75 and older were consistent with findings from a previous study with oral bisphosphonates, which reported a reduction in the incidence of vertebral and nonvertebral fractures.³¹⁻³³ A study evaluating the effect of age on the antifracture efficacy of alendronate revealed no effect of age on the significant relative risk reductions of clinical fractures with alendronate compared with placebo, although the absolute risk reductions for vertebral and hip fractures in women aged 75 and older with low BMD increased with age,^{34,35} implying a possible improvement in the cost-effectiveness of bisphosphonate treatment in elderly patients.

Patients aged 75 and older showed a reduction in incidence of all but hip fractures, whereas those younger than 75 showed a reduction in incidence of all fracture types. This may be due to the increasing influence of nonskeletal risk factors for these types of fractures, such as falling with older age. Moreover, this was a post hoc analysis, and therefore the sample size used for the analysis was not statistically powered to detect risk reduction for hip fracture within the specified subgroup (≥ 75). Therefore, in the current analysis of the effect of zoledronic acid according to age, the focus was specifically on vertebral and nonvertebral fractures and not on hip fracture. This remains a limitation of the study, because this was a post hoc analysis that involved two different patient populations.

Overall, the robust effect of ZOL treatment on clinical vertebral fractures in patients aged 75 and older in this analysis supports the concept that ZOL treatment effectively addresses the “skeletal fragility” component of fracture risk, even in relatively older patients with osteoporosis. In the HORIZON Pivotal Fracture Trial, patients with a BMD T -score of -2.5 or less at the femoral neck, with or without evidence of existing vertebral fracture, or a T -score of -1.5 or less, with radiological evidence of vertebral fracture, were included. In the HORIZON Recurrent Fracture Trial, patients with a recent hip fracture were included. Thus, whether elderly women with low BMD (-2.49 to -1.5) and no prevalent vertebral fractures would have a significant reduction in fracture incidence from treatment remains unknown.

mg showed a favorable safety profile in Treatment with ZOL 5 elderly patients. The overall incidence rates of AEs, SAEs, and deaths were comparable in ZOL and placebo across both age groups. The incidence of postdose symptoms within 3 days of study drug infusion, such as mg, pyrexia, myalgia, and influenza-like illness, were higher with ZOL 5 as reported previously.^{25,28} In contrast to the findings reported in the HORIZON Pivotal Fracture Trial,^{25,28} the incidence rate of atrial fibrillation events was similar between groups in this analysis.

Adherence to osteoporosis medications is an important problem in the treatment and care of elderly patients.³⁶⁻³⁸ Approximately 20% to 50% patients abandon their treatment within 6 to 12 months after initiating therapy.³⁷ Nonadherence has been shown to compromise the treatment efficacy on fracture risk reduction and thus significantly increase related medical costs.^{19,24} The reasons associated with nonadherence in older adults include side effects, therapy administration frequency, and specific administration mg provides an requirements. The once-yearly intravenous ZOL 5 alternative treatment option, which would increase adherence, especially in older adults, by avoiding repeated and complicated dosing regimens.

CONCLUSION

Further to the benefits achieved with once-yearly intravenous infusion mg in both HORIZON landmark trials, the current ad hoc pooled of ZOL 5 analysis showed that this treatment was safe and effective in elderly postmenopausal women with osteoporosis aged 75 and older. Moreover, by ensuring full effect for at least 12 months, this therapy may greatly improve osteoporosis treatment in geriatric practice.

INFORMED CONSENT: written informed consent was taken from patients .

ETHICAL APPROVAL: ethical committee approval was taken from the institutional committee of ethics .

SOURCE OF FUNDING- funding source was self

CONFLICT OF INTEREST – there was no conflict of interest

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