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Intravenous Zoledronate 4 mg for the treatment of post-menopausal osteoporosis: A prospective open-labeled study

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ABSTRACT

Background: Zoledronate 5 mg intravenous (IV) annually is approved for treatment of post-menopausal osteoporosis. Zoledronate 4 mg which is approved for the treatment of cancer related hypercalcemia can be an alternative for Asian women who have smaller stature.
Objectives: To examine the efficacy and safety of Zoledronate 4 mg IV annually for the treatment of post-menopausal osteoporosis.
Method: A prospective open-labeled study was performed on 33 post-menopausal osteoporosis patients. All patients received a dose of IV Zoledronate 4 mg. Bone mineral density (DXA) was examined at baseline and 12 months after treatment. Beta-C-terminal telopeptide (β-CTX) and procollagen type-1-amino-terminal propeptide (P1NP) were obtained at baseline, 6, and 12 months after treatment. Adverse events were recorded.
Results: The mean age (SD) was 69 (11.1) years old. The lumbar spine BMD increased significantly from the mean (SD) lumbar spine BMD at baseline of 0.833 (0.132) g/cm^2 to 0.862 (0.132) after treatment ($p = 0.001$). There was no significant differences in total hip and femoral neck BMDs between baseline and 12 months after treatment. The β-CTX and P1NP decreased significantly from the mean (SD) of 0.44 (0.24) and 55.57 (38.6) ng/ml at baseline to 0.21 (0.11) and 27.26 (10.95) ng/ml after treatment ($p < 0.001$), respectively. Infusion reaction was observed in five patients. There were two fractures observed.
Conclusion: Zoledronate 4 mg improved lumbar BMD and decreased β-CTX and P1NP significantly after 12 months of treatment. Zoledronate 4 mg could be an alternative to Zoledronate 5 mg for the treatment of post-menopausal osteoporosis.

1. Introduction

Osteoporosis is common among postmenopausal women. Fracture significantly increases the morbidity and mortality of affected patients (Johnell and Kanis, 2006; Lyles et al., 2007). Oral bisphosphonates reduce the incidence of fractures (Black et al., 1996; Qaseem et al., 2017). However, poor adherence and compliance to oral bisphosphonates limited their anti-fracture efficacy (Siris et al., 2006). Siris, et al., reported that adherence to bisphosphonate therapy was associated with significantly fewer fractures at 24 months. Therefore, intravenous bisphosphonate such as Zoledronate is preferred in non-compliant patients. Once-yearly infusion of Zoledronate 5 mg has been proven to reduce the risk of vertebral, hip and nonvertebral fractures and to increase lumbar spine and total hip bone mineral density (BMD) over 3 years in postmenopausal women with osteoporosis (Black et al., 2007).

Zoledronate 5 mg costs more than 15,000 baht (460 US dollars/405 Euros) annually and must be imported. This treatment is not covered by Thailand's Universal Coverage Scheme, so some patients were unable to afford it. Zoledronate 4 mg IV is approved to treat Paget's disease of bone, hypercalcemia of malignancy (HCM) and used as an adjunctive treatment to antineoplastic therapy for the treatment of bone metastases of solid tumors and osteolytic lesions of multiple myeloma. Furthermore, the lower dose of zoledronate might be more appropriate for patients with Asian ethnicity who have smaller stature than those with Caucasian ethnicity as compared to the regular 5 mg dosage of zoledronate.

Zoledronate 4 mg costs 3200 baht annually (98 US dollars/86 Euros) and is manufactured in Thailand. If the effectiveness of the 4 mg zoledronic acid infusion can be proven, an alternative option can be made available for patients who cannot afford the standard treatment

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particularly relevant for patients with Asian ethnicity.

The objective of this study was to examine the efficacy and safety of Zoledronate 4 mg IV annually for the treatment of post-menopausal osteoporosis which has not been studied in Thailand.

2. Material and methods

This was a 12-month, single-center, open-labeled, prospective study. It was approved by the Institutional Board Review of the Royal Thai Army Medical Department (Approval number IRBRTA 1061/2561) on June 27th, 2018 and conducted in accordance with the Declaration of Helsinki and followed the International Conference for Harmonization Guidelines for Good Clinical Practice. Written informed consent was obtained from each patient before study participation.

Participants in the study were postmenopausal women from the Internal Medicine and Rheumatology Outpatient Clinic, Phramongkutklao Hospital between July 2018, and December 2019 who met the criteria to receive osteoporotic treatment according to the Thai Osteoporosis Foundation (TOPF) position statements on management of osteoporosis (Songpatanasilp et al., 2016). In all the women, menopause had occurred at least five years previously, either naturally or as the result of bilateral oophorectomy. Osteoporosis is defined according to the WHO operational definition of postmenopausal osteoporosis (T-score at the lumbar spine or hip of less or equal to −2.5) (Kanis et al., 1994).

Exclusion criteria included patients who previously received anti-resorptive treatment including bisphosphonate, estrogen replacement therapy, calcitonin and raloxifene, moderate to severe renal impairment (GFR < 35 mL/min estimated by CKD-EPI equation, (Levey et al., 2009) allergic to bisphosphonates, planning for invasive dental surgery within 12 months after Zoledronate infusion, history of atrial fibrillation, history of hyperparathyroidism, vitamin D insufficiency and evidence of secondary osteoporosis. Patients with vitamin D insufficiency and deficiency (Bouillon and Carmeliet, 2018) were given ergocalciferol replacement to achieve the optimal 25(OH)D level of 30 ng/mL or more prior to enrollment. All patients received calcium carbonate 1500 mg per day and ergocalciferol 20,000 IU per week throughout the study.

All patients received a single dose of 4 mg of Zoledronate given as a 15 to 30 min intravenous infusion in 100 mL of 0.9% NaCl. Each vial (5 mL) contains Zoledronic acid monohydrate equivalent to Zoledronic acid anhydrous 4 mg. All patients received 2 glasses of water and 1 tablet of 500 mg-acetaminophen 30 min prior to Zoledronate infusion. Zoledronate 4 mg was manufactured by Siam Pharmaceutical Company.

Baseline demographics including age, sex, previous fractures, co-morbidities and current medications were recorded. The 10-year risk for major osteoporotic fracture and hip fracture were assessed by FRAX (Kanis et al., 2008). Secondary causes of osteoporosis were investigated according to the TOPF position statements on management of osteoporosis (Songpatanasilp et al., 2016). Complete blood count (CBC), Blood urea nitrogen (BUN), creatinine, serum calcium, serum phosphate, serum 25(OH)D or vitamin D level, thyroid function test and parathyroid hormone were examined prior to enrollment into the study.

Bone mineral density was measured at the lumbar spine, femoral neck, and total hip by Dual-energy X-ray Absorptiometry (DXA) (GE-lunar iDXA) at baseline and 12 months after treatment. Vertebral fracture assessment (Genant et al., 1993) and trabecular bone score (TBS) (Silva et al., 2014) were also examined at baseline and 12 months in all patients. Morphometric vertebral fractures were prospectively evaluated using Genant's semi-quantitative method (Genant et al., 1993). Incident morphometric vertebral fractures were defined as a reduction in vertebral height of 4 mm and at least 20% by quantitative morphometry or increase of one severity grade or more on semi-quantitative analysis. Trabecular bone scores (TBS) have been established into 3 categories; a) TBS ≤ 1.2 defined as a degraded micro-architecture; b) TBS between 1.2 and 1.35 defined as a partially degraded microarchitecture and c) TBS ≥ 1.35 considered as a normal TBS (Silva et al., 2014).

Serum bone turnover markers including beta-C-terminal telopeptide (β-CTX) and total procollagen type 1 amino-terminal propeptide (P1NP), serum calcium and serum phosphate were measured at baseline, 6 and 12 months after treatment. P1NP and β-CTX were measured by electrochemiluminescence assay (ECLIA; Elecsys, Roche Diagnostics, Mannheim, Germany).

The proportions of patients, who had achieved the Least Significant Change (LSC) defined as an increase more than 0.028 g/cm^2 of hip and spine BMD and bone turnover markers decrease ≥30% of β-CTX and ≥ 25% of P1NP (Schousboe and Bauer, 2012; Vasikaran et al., 2011), compared to baseline values were calculated. Adverse events and fracture occurrences were recorded during the study period.

Continuous variables are presented as mean and standard deviation (SD) and categorical as observed number and percentage. The differences in BMD, CTX, P1NP and TBS between baseline, and post-treatment were compared using a paired *t*-test. All statistical analyses were performed by using IBM SPSS statistics for Windows version 22.0. Statistical significance was defined as a p-value <0.05.

3. Results

A total of 36 post-menopausal women with osteoporosis were enrolled. Two patients were lost to follow-up and one patient withdrew from the study after 2 months of Zoledronate infusion because of the infusion reaction. The mean (SD) age was 69 (11.1) years old. The mean (SD) BMI was 21.3 (3.1) kg/m^2. 51.6% of patients had osteoporosis at both lumbar spine and hip. The mean (SD) T-scores at lumbar spine and femoral neck were -2.89 (1.13) and -2.68 (0.52), respectively. The mean (SD) risks of 10-year probability of hip fracture and other major osteoporotic fractures were 3.6 (3.5) and 9.1 (5.4), respectively. Four patients (12.1%) had previous fractures; two with vertebral fractures, one with a hip fracture and one with a distal radius fracture. All patients had normal serum calcium levels and adequate 25(OH)D levels with mean (SD) of 25(OH)D 39.3 (21.5) ng/mL. The baseline characteristics data are shown in Table 1.

Table 1
Baseline characteristics of patients.

Demographic and baseline characteristic data	Of 33 patients
Age (years): mean ± SD	69 ± 11.1
Body mass index (kg/m^2): mean ± SD	21.3 ± 3.1
Serum calcium level (mg/dl)	9.2 ± 0.4
25(OH)D level (ng/ml)	39.3 ± 21.5
Glomerula filtration rate (mL/min)	59.5 ± 21.6
Site of osteoporosis diagnosis: number (%)	
Hip (total hip or femoral neck)	6 (18.2)
Lumbar Spine	7 (21.2)
Both hip and Lumbar spine	17 (51.6)
Bone mineral density (g/cm^2): mean ± standard deviation	
Femoral neck	0.662 ± 0.072
Total hip	0.737 ± 0.088
Lumbar spine	0.833 ± 0.132
T-score: mean ± standard deviation	
Femoral neck	−2.68 (0.52)
Total hip	−2.09 (0.68)
Lumbar spine	−2.89 (1.13)
FRAX: number (%)	
10-year probability of hip fracture ≥ 3%	13 (39.4)
10-year probability of other major osteoporotic fracture ≥ 20%	2 (6.1)
FRAX: mean ± standard deviation	
10-year probability of hip fracture	3.6 (3.5)
10-year probability of other major osteoporotic fracture	9.1 (5.4)
Previous fracture: number (%)	
Vertebral	2 (6.1)
Hip	1 (3.1)
Wrist	1 (3.1)
Trabecular bone score (%)	
<1.2	8 (24.2)
1.2–1.35	15 (45.6)
>1.35	9 (27.3)

The mean (SD) lumbar spine BMDs significantly increased from 0.833 (0.132) g/cm^2 to 0.862 (0.132) g/cm^2 after 12 months of Zoledronate infusion ($p = 0.001$). In the hip region, there was no difference in BMD before and 12 months after treatment. The mean (SD) total hip BMDs before and after 12 months of Zoledronate infusion were 0.737 (0.088) and 0.747 (0.09) g/cm^2 ($p = 0.05$). The mean (SD) femoral neck BMDs before and after 12 months of Zoledronate infusion were 0.662 (0.072) and 0.671 (0.092) g/cm^2 ($p = 0.378$). The proportions of patients who achieved the LSC at the lumbar spine, total hip and femoral neck were 51.5%, 27.3% and 24.2%, respectively. The BMD results were depicted in Table 2.

The bone turnover markers were decreased significantly at 6 and 12 months after treatment. The mean (95% confidence interval: CI) P1NPs were 55.57 (40.89–70.26), 27.28 (20.96–33.60), and 27.26 (22.92–31.59) at baseline, 6 months and 12 months after treatment with the p values of <0.001 at 6 and 12 months after treatment. The mean (95% CI) CTXs were 0.44 (0.35–0.52), 0.15 (0.11–0.19), and 0.21 (0.17–0.25) at baseline, 6 months and 12 months after treatment, respectively with the p values of <0.001 at both 6 and 12 months after treatment. The proportion of patients who achieved the LSC of P1NP and β-CTX changes were 83.3% and 76.7%, respectively. The bone markers' data were shown in Fig. 1.

There were two new fractures observed in two patients during the study. One was at the distal radius, and another was the vertebral fracture. No serious adverse events or death were found. Post-infusion reaction was found in 5 patients including 3 patients with fever (9.1%) and 2 patients with myalgia (6.1%). All of which were mild and spontaneously resolved within a few days. No arrhythmia, avascular necrosis of the jaw, atypical femoral fracture or symptomatic hypocalcemia was detected during the study period.

4. Discussion

This study was conducted to examine the efficacy and safety of a generic 4-mg Zoledronate once yearly for treating post-menopausal osteoporosis. Our study demonstrated that a single infusion of 4 mg of Zoledronate improved BMD at lumbar spine, and decreased bone turnover markers including P1NP and β-CTX. There were two fractures during the study. The rate and severity of adverse events were similar to the branded Zoledronate 5 mg (Black et al., 2007).

Percent change in BMD lumbar spine in the present study was similar to previous studies as shown in Table 3. However, the BMD at the hip region including total hip and femoral neck BMDs were not significantly increased after 12 months of a single dose of a generic 4-mg of Zoledronate. This could be due to the short follow-up time (12 months) in the present study. Repeated dose annually and a longer follow-up period may enhance the effects of a generic 4-mg of Zoledronate on the total hip and femoral neck BMDs. Hip bone has less trabecular bone and less bone turnover than the bone in the lumbar spine. Therefore, the total hip and femoral neck BMDs had responded less to anti-resorptive agents especially bisphosphonates than the BMD at the lumbar spine (Black et al., 2007; Grey et al., 2014). Increases in total hip and femoral neck BMDs usually take longer than in the lumbar spine BMD after bisphosphonate treatment (Kunupakan et al., 2018). These findings are consistent with other randomized controlled trials that examined the efficacy of bisphosphonates in post-menopausal osteoporosis (Black et al., 2007).

Table 2
Bone mineral density, trabecular bone score and bone markers before and after treatment.

Variables (mean ± standard deviation)	Baseline	12 months after Zoledronate 4 mg treatment	p-value
Bone mineral density, (g/cm^2)			
Hip			
Femoral neck	0.662 ± 0.072	0.671 ± 0.092	0.378
Total hip	0.737 ± 0.088	0.747 ± 0.09	0.05
Lumbar spine	0.833 ± 0.132	0.862 ± 0.132	0.001
Trabecular bone score	1.27 ± 0.10	1.27 ± 0.10	0.697
Bone markers (IU/mL)			
Total procollagen type 1 amino-terminal propeptide (P1NP)	55.57 ± 38.6	27.26 ± 10.95	< 0.001
Beta-C-terminal telopeptide (β-CTX)	0.44 ± 0.24	0.21 ± 0.11	< 0.001

The BMD gain from zoledronate 4 mg was quite reassuring for the fracture prevention. The increment in BMD has shown to be a surrogate for fracture prevention in many osteoporosis treatment studies (Black et al., 2020; Bouxsein et al., 2019; Eastell et al., 2021). The greatest fracture reduction occurred in those who gained BMD, although those with stable BMD still had fewer fractures than those who lost BMD (Hochberg et al., 1999). For a change in BMD to be considered significant, it should be greater than the LSC for the densitometer. The proportions of patients who achieved the LSC of BMD in the present study were 51.5% at the lumbar spine, but only 27.3% at the total hip and 24.2% at the femoral neck. This result reflected the effect of Zoledronate which increased the BMD of the lumbar spine more than in the hip region.

In terms of bone turnover marker suppression, our study found that the most suppression occurred at 6 months which was sustained up to 12 months. This is consistent with the data from other studies (Black et al., 2007; Kunupakan et al., 2018). The proportions of patients who achieved the LSC of serum P1NP and β-CTX were 83.3% and 76.7%, respectively.

Grey et al. published a study of 50 postmenopausal women who were randomized to receive a single 5 mg dose of Zoledronate or placebo. After 5 years of follow up, bone turnover markers were decreased to premenopausal levels, and bone density at lumbar spine improved 4–5% (Grey, 2016; Grey et al., 2012) and a redosing of Zoledronate 5 mg after 5.5 years prevents bone loss over almost 11 years. Greenspan et al., conducted a randomized controlled trial in the debilitated elderly women in a health service facility, and a single dose of 5 mg Zoledronate produced increases in bone density and reduction in bone turnover markers that were sustained during 2 years of follow up, without evidence of treatment offset (Greenspan et al., 2015; Grey, 2016). Grey et al. studied 180 post-menopausal women with osteopenia (Grey et al., 2012). Those patients were randomized to receive a single dose of different regimens of Zoledronate including Zoledronate 1 mg, Zoledronate 2.5 mg, or Zoledronate 5 mg, or placebo. All patients had BMDs and bone turnover markers followed-up up to 24 months. There were similar changes of bone turnover marker and BMDs in the 2.5 mg and 5 mg Zoledronate patients. After 2 years, there had been some offset of the effects of the 1 mg dose, but the 2.5 mg dose produced comparable effects to those of the 5 mg dose (Grey, 2016; Grey et al., 2014). The evidence for very prolonged anti-resorptive actions of Zoledronate is also apparent in 43 men with HIV infection. They were randomized to two annual doses of placebo or 4 mg intravenous Zoledronate. Zoledronate sustainably increased bone density and decreases in markers of bone turnover for at least 5 years after drug administration, without evidence of offset (Bolland et al., 2012; Grey, 2016). Finally, Kunupakan et al. found that a single infusion of 4 mg of Zoledronate increased the lumbar spine BMD and reduced bone turnover markers in Thai scleroderma patients with osteoporosis (Kunupakan et al., 2018). Those data and the results from our study suggested that the lower dose or longer interval of Zoledronate could be as efficacious as the standard 5 mg Zoledronate IV annual dose. The lower dose of Zoledronate regimen might be of particularly interest in Thai and Asian patients, who typically have smaller stature than those of Caucasians.

Common adverse reactions of Zoledronate infusion include: myalgia, pyrexia, arthralgia, influenza-like illness, and nausea (Strampel et al.,

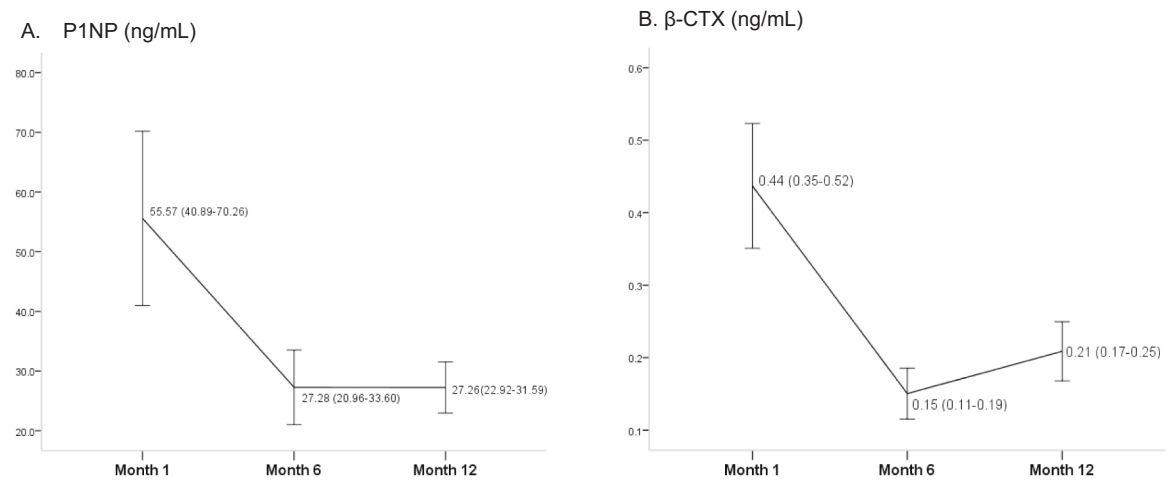

Fig. 1. The figure shows the changes of serum bone markers including A. total pro-collagen type 1 amino-terminal pro-peptide (P1NP) and B. *beta*-C-terminal telopeptide (β-CTX) before and after treatment with a single dose of Zoledronate 4 mg intravenously, mean (95% confidence interval).

Table 3
Comparisons of studies that have examined the efficacy of various doses of Zoledronate.

BMD	Present study	Black DM et al. 2007 (Black et al., 2007)	Study by Grey A et al. 2014 (Grey et al., 2014)	Greenspan SL et al. 2015 (Greenspan et al., 2015)	Bolland MJ et al. 2012 (Bolland et al., 2012)	Kunupakan S MA et al. 2018 (Kunupakan et al., 2018)
Patients (n)	33	7765	180	181	43	30
Inclusion criteria	Postmenopausal with BMD T score of −2.5 or less at either lumbar spine or hip	Postmenopausal with BMD T score of −2.5 or less at femoral neck	Postmenopausal with BMD T score between −1 and −2.5 at either lumbar spine or total hip	≥65 years old frail women with BMD T score of −2.0 at spine, hip or radius	HIV-infected men with BMD T score below 0.5 at the lumbar spine or total hip	≥15 years old systemic sclerosis patients With BMD T score of −2.5 or less at lumbar spine or total hip
Zoledronate	4 mg	5 mg	1, 2.5, 5 mg	5 mg	4 mg	4 mg
Treatment duration (months)	12	36	24	24	72	12
BMD changes (95% CI) (Lumbar spine)	3.7% (1.7 to 5.7%)	6.71% (5.69 to 7.74%)	4.4, 5.5, 5.3%	4.5%	3.5% (0.7 to 6.7%)	6.76%
BMD changes (95% CI) (Total hip)	1.5% (0 to 3%)	6.02% (5.77 to 6.28%)	2.6, 4.4, 4.7%	2.6%	3.4% (1.4 to 5.4%)	4%

2007). The adverse events of Zoledronate 4 mg were similar to Zoledronate 5 mg from other studies. In our study, patients reported the following: fever - 3 (9.1%) and myalgia - 2 (6.1%).

There were limitations in this current study. The number of patients was small, and the follow-up time was too short to demonstrate BMD changes at the hip site, anti-fracture efficacy and long-term safety of Zoledronate 4-mg annually. In addition, there was no placebo or control group in this study. In the future, we plan to recruit more patients and increase follow-up time to 3 years and administer 2 more doses of Zoledronate 4-mg.

5. Conclusion

Zoledronate-4-mg infusion annually improved lumbar BMD and decreased CTX and P1NP significantly after 12 months of treatment. However, there was no difference in total hip BMD at baseline and after treatment. This may increase an adherence to long-term treatment and potentially increase access to treatment in Thai Universal Coverage Scheme patients. Proven effectiveness of Zoledronate 4 mg makes it as a good alternative for Asian patients who have small stature, for patients who are unable to afford the standard treatment of 5 mg for the treatment of post-menopausal osteoporosis.

Availability of data and material (data transparency)

Available.

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CRediT authorship contribution statement

TA has contributed to acquisition of data, data curation, investigation, and drafting the manuscript.

SC has contributed to conceptualization, visualization, supervision, interpretation of data, and writing - review & editing the drafted manuscript and funding acquisition.

All authors have given final approval of the version to be published and agree to be accountable for all aspects of the work.

Declaration of competing interest

There were no financial or non-financial competing interests relevant to the published content. All authors declare no conflict of interests that might influence the result of this study.

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