Original Article

The Effect of 4 Milligrams Intravenous Zoledronic Acid Once Yearly on Bone Mineral Density and Biochemical Bone Markers In Systemic Sclerosis Patients with Osteoporosis

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Background: Systemic sclerosis [SSc] is associated with increased risks of osteoporosis and fragility fracture. Oral bisphosphonates is contraindicated in SSc patients due to increased risk of esophagitis. Although 5 mg intravenous zoledronic acid [Zol] has been approved for treatment of osteoporosis; however, using this drug is often limited due to its high cost and medical reimbursement limit in Thailand.

Objective: To examine the effect of Zol (4 mg) on bone mineral density [BMD] and bone turnover markers in SSc patients with osteoporosis.

Materials and Methods: An open-labeled study was designed**.** SSc patients with osteoporosis from Scleroderma Clinic, Khon Kaen University, Thailand were recruited. Lumbar spine and total BMD, and spinal radiography were performed at baseline and 12 months. Serum N-terminal propeptide of type I Pro-collagen [P1NP] and C-telopeptide of type I collagen [CTX] were evaluated at 0, 3, 6, and 12 months after treatment.

Results: Twenty-six patients were recruited for the final analysis. At 12 months, Lumbar spine BMD increased significantly with Zol (6.76%, $p<0.001$), while total hip BMD was improved but not reach the statistical significance when compared with baseline (4%, $p = 0.272$). Both P1NP and CTX decreased significantly at 3 months and sustained to 12 months when compared with baseline. There was no new or worsening fractures during the study. Minor adverse events were observed but transient and were resolved within a few days.

Conclusion: Single infusion of 4 mg Zol increased the lumbar spine BMD and reduced bone turnover markers in SSc patients with osteoporosis. This finding suggests that low dose Zol (4 mg) might be an alternative treatment for osteoprosis in SSc patients.

Keywords: Osteoporosis, Systemic sclerosis, Zoledronic acid

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Systemic sclerosis [SSc] is recognized as a risk factor of osteoporosis and fragility fracture. The prevalence of osteoporosis in SSC varied from 19.4 to 42%[1-3],while the incidence of fracture among SSc patients with osteoporosis was 35%[1], which was high and comparable with rheumatoid arthritis (32%). In Thailand, a preliminary report on prevalence of osteoporosis in adult SSc patients was 29.4%[4].

Despite oral bisphosphonates [BPs] commonly use as the first line treatment for osteoporosis. However, in SSc patients with esophageal dysmotility, oral BPs is not recommend due to increase risk of esophagitis[5]. Therefore, alternative treatments, i.e., intravenous form of BPs or non-BPs antiosteoporotic drugs are preferable instead of oral BPs. Once yearly intravenous zoledronic acid [Zol] is

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one of the treatment for osteoporosis in clinical practice[6]. In postmenopausal women, 5 mg of Zol infusion annually increased bone mineral density [BMD] at lumbar spine and hip, and also decreased fractures including vertebral, non-vertebral and hip fractures[7]. However, the 5 mg of original Zol for osteoporosis treatment in Thailand is limited due to high cost and reimbursement policy. Moreover, Thais has smaller body built compared with Western population. Therefore, an availability of 4 mg of generic Zol is challenged for osteoporosis treatment among Thai SSc patients. This study was designed to examine the effect of single dose of generic 4 mg intravenous Zol on BMD, bone turnover markers [BTMs] and safety in Thai SSc patients with osteoporosis.

Materials and Methods

Study design and subjects

An open-labeled study was designed and SSc patients were recruited from the Scleroderma clinic of Srinagarind Hospital, Thailand, between October 2013 to October 2015. SSc patients who aged of 15 years or more were enrolled if they had a BMD T-score of -2.5 or less at lumbar spine (L1-L4) or total hip. Patients with history of previous treatment with BPs or other antiosteoporotic agents, a creatinine clearance less than 35 mL per minute (estimated by CKD-EPI equation)[8], pregnancy or lactation, have invasive dental surgery plan within 3 months after infusion, history of atrial fibrillation, vitamin D insufficiency or deficiency, history of hyperparathyroidism or hypoparathyroidism, hyperthyroidism or hypothyroidism, rheumatoid arthritis, mixed connective tissue disease, and uncorrectable electrolyte imbalance, i.e., hypocalcemia, hypomagnesemia, hypophosphatemia were excluded from the study. During the study period, all recruited patients were assigned to receive 15-minute intravenous injection of generic Zol (4 mg). All patients received oral calcium (1,000 to 1,500 mg) and vitamin D_2 (20,000 IU per week). The protocol was approved by Khon Kaen University Institute of Research Ethics Committee.

Measurements

Bone mineral density [BMD] was measured at the lumbar spine, and total hip by dual energy x-ray absorptiometry [DXA] (Lunar Prodigy model, Lunar Corp., Madison, WI) at baseline and 12 months. A lateral thoraco-lumbar [T-L] x-ray radiograph was taken at baseline and 12 months or at the time that patients presents with new back pain. Vertebral bodies from T4 to L4 levels were assessed to define vertebral fracture. Radiographic (morphometric) vertebral fracture (referred to as vertebral fracture in the present study) was evaluated using the Genant's semi-quantitative method[9] and standard method. 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. Levels of serum N-terminal propeptide of type I pro-collagen [P1NP] and C-telopeptide of type I collagen [CTX] in fasting samples were measured at baseline, at 3, 6 and 12 months after treatment. The proportions of patients, who had achieved the Least Significant Change [LSC] in BMD (>0.029 g/cm^2 of hip and lumbar spine BMD) and bone turnover markers[10] (decreased >30% and >25% for P1NP and CTX, respectively), were calculated. Adverse events were recorded during the study period.

Statistical analyses

Continuous variables are presented as mean and standard deviation [SD] and categorical variables as observed number and percentage. The difference in BMD between baseline and post-treatment were compared using paired t-test, while the differences in BTMs were compared by repeated measures ANOVA. All statistical analyses were performed by using STATA software version 10.1 (College Station, Texas, USA) with the right of Khon Kaen Univesity. Statistical significance was defined as a p-value <0.05.

Results

A total of 30 SSc patients were enrolled, and 4 patients were excluded due to incomplete data of BTMs, left 26 (86.7%) patients for the final analysis (8 men and 18 women). The mean age and BMI was 57.5 years and 20.8 kg/m^2, respectively. Of 84.6% (22/26) of patients was diagnosed as diffuse cutaneouse SSc; and osteoporosis at the lumbar spine was more common than hip region in the present study (Table 1).

After 12 months of 4 mg Zol treatment, BMD at the lumbar spine was increased 6.76% from baseline [0.754 g/cm^2 (0.474 to 0.886) at baseline to 0.804 g/cm^2 (0.519 to 1.026) at 12 months], with mean difference of 0.051$\pm$0.22, p-value <0.001. While BMD at the total hip was also increased 4% from baseline [0.700 g/cm^2 (0.290 to 0.993) at baseline to 0.718 g/cm^2 (0.270 to 0.990) at 12 months], with mean difference of 0.028$\pm$0.22, p = 0.272. The proportions of patients who achieved the LSC at the lumbar spine and total hip were 69.2% and 34.6%,

respectively.

The levels of serum P1NP were significantly decreased 55.9%, 51.4% and 43.0% at 3-, 6- and 12-month compared with baseline, while the levels of serum CTX were significantly decreased 57.1%, 48.2% and 53.6% at 3-, 6- and 12-month compared with baseline as shown in Figure 1. According to the LSC, in the first 3 month, 84.6% (22/26) and 80.8% (21/26) of patients had serum P1NP and CTX decreased to the LSC level, respectively, while 57.7% (15/26) and 61.5% (16/26) of patients had serum P1NP and CTX decreased to the LSC level through the treatment period. Of 7.7% (2/26) and 19.2% (5/26) of patients that P1NP and CTX were not decreased to the LSC levels at any times of treatment.

At baseline, 69.2% (18/26) of patients had morphometric vertebral fractures. There was no new or worsening of vertebral fracture and other fragility fractures along the study period. In this study, the serious adverse events or death were not found. Post-infusion symptoms were found in 6 patients including fatigue (1/26, 3.8%), fever (3/26, 11.5%), and myalgia (2/26, 7.6%); however, all adverse events were transient and spontaneously resolved within a few days. None of the patients developed atrial fibrillation, osteonecrosis of the jaw, atypical femoral fracture or symptomatic hypocalcemia. There was one case developed congestive heart failure, resulting from the underlying cardiomyopathy and recovered after an appropriate treatment.

Discussion

Patients with SSc are at risk of osteoporosis and fragility fracture. This study was conducted to assess whether treatment with 4 mg of generic Zol once yearly is adequate for treating osteoporosis in patients with SSc. Our study demonstrated that single infusion of 4 mg Zol improved BMD at both lumbar spine and total hip, decreased BTMs without new or worsening of fractures and acceptable minor adverse events at 12 months after treatment. BMD increased significantly at lumbar spine (6.76%, mean difference: 0.051±0.22, $p<0.001$), and trend to be increased at total hip (4%, mean difference 0.028±0.22, $p=0.272$) as compared with baseline. Both BTMs including serum P1NP and CTX decreased significantly at 3 months after infusion and sustained until 12 months. These findings appear to ensure that SSc patients with osteoporosis will have a favorable treatment effect for at least 12 months.

Since there was no clinical study of bisphosphonates on BMD in SSc patients with osteoporosis in the literature; however, in our current study, changes in BMD are similar to results those

Table 1. Characteristics of study patients

Demographic data	n = 26
Mean ± SD of age, years	57.5±8.9
Female sex	18 (69.2)
Postmenopausal female	15 (83.3)
Mean ± SD of body mass index (kg/m^2)	20.8±4.6
Types of systemic sclerosis	
Diffuse cutaneous systemic sclerosis	22 (84.6)
Limited cutaneous systemic sclerosis	4 (15.4)
Duration of disease	
1 to 3 years	6 (23.1)
3 to 5 years	9 (34.6)
5 to 10 years	8 (30.8)
More than 10 years	3 (11.5)
Site of osteoporosis diagnosis	
Hip	3 (11.5)
Spine	17 (65.4)
Both hip and spine	6 (23.1)

Data presented as number (percentage) unless indicated otherwise

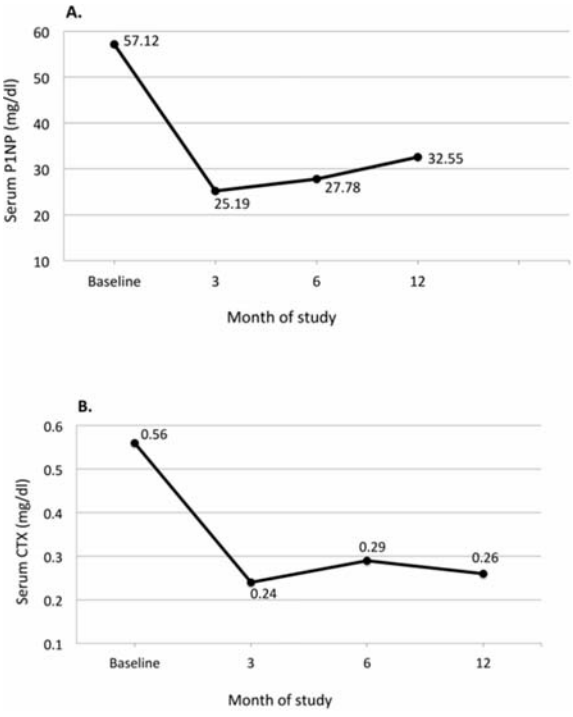

Figure 1. Effect of zoledronic acid on bone turnover markers, A: serum P1NP and B: serum CTX.

observed in postmenopausal women in previous studies. An increase of BMD at lumbar spine and hip at 12 months are comparable with intravenous Zol at various doses (0.25, 0.5 or 1.0 mg every 3 months, 2.0 mg every 6 months, or a single annual 4.0 mg dose), which were 4.3 to 5.1% at lumbar spine and 3.1 to 3.5% at femoral neck at 12 months[11], 5 mg of intravenous Zol (~3.9 and 6.7% at 12- and 36-months of lumbar spine, ~2.9 and 6.0% at 12- and 36-months of total hip, respectively)[7], 150 mg of daily pamidronate (5% at lumbar spine and 3% at femoral neck, at 12 months)[12], 10 mg of daily alendronate (5% at lumbar spine and 3% at femoral neck, at 12 months)[13], or 5 mg of daily risedronate (3% at lumbar spine and 2% at femoral neck, at 12 months)[14]. The reductions in BTMs at 12 months in the present study were similar to those seen with 10 mg of daily alendronate[15-17], 5 mg of daily risedronate[14], or 2.5 to 5 mg daily of ibandronate[18] and also 4 or 5 mg annually of intravenous Zol[7,11]. Moreover, the suppression of BTMs in the present study was highest at 3 months and sustained to 12 months, which was consistent with previous study. Results from the Horizon Pivotal Fracture trial demonstrated that 5 mg of Zol was associated with decreased in serum P1NP [58% (95% CI 55 to 60)] and CTX [59% (95% CI 55 to 63)] at 12 months[7] as well as 4 mg of Zol decreased 49 to 52% in serum CTX and 54 to 65% in the ratio of urinary N-telopeptide to creatinine, respectively[11].

The proportions of patients who achieved the LSC of BMD in the present study were 69.2% at lumbar spine, but only 34.6% at total hip. These results have been observed in previous studies in clinical practice. It takes longer period to increase the BMD of the hip region than in the lumbar spine. We also observed that more than 80% and 50% of patients achieved the LSC targets for serum P1NP and CTX at 3- and 12-month after treatment, respectively. Only few patients [7.7% (2/26) for P1NP and 19.2% (5/26) for CTX) did not reach the LSC targets at any times of treatment. Hershman[18] reported that BTMs were not suppressed with 4 mg of Zol in premenopausal women undergoing adjuvant chemotherapy. In contrast with present findings, all patients who failed to suppress BTMs in our study were postmenopausal women and their baseline BTM levels were low as in premenopausal range at baseline. Therefore, suppression in BTMs may not be observed in these patients. Allanore[19] reported that only half of SSc patients had a higher serum CTX level than healthy controls. High serum CTX levels were associated with the disease activity, diffuse cutaneous SSc, acute phase reactants (i.e., C-reactive protein, erythrocyte sedimentation rate) and also positive antitopoisomerase I autoantibodies).

Although once yearly 5 mg of Zol infusion is approved for treatment of osteoporosis, the optimal dosing regimen of this medication has not been evaluated in Thai population who have small body frame. The optimal dosing regimen in previous studies on BMD and BTMs were conflict. Substantial increases in BMD were observed in patients who received 4 mg of Zol even significant reduction in BTMs. Moreover one third of patients did not achieved an optimal reduction in bone-specific alkaline phosphatase, while optimal response has been observed in serum CTX[20]. However, in the 12-month phase II study of 4 mg Zol was showed to be equally effective in increasing BMD and decreasing BTMs which was consistent with the present study[11].

Once yearly 4 mg of Zol was generally well tolerated. In the present study, minor adverse events has been observed; however, all of which were mild and spontaneously resolved within a few days, which was similar those occurred previously in patients receiving intravenous aminobisphosphonates. Within the 12-month study period, there was no new osteoporotic fractures or worsening of fractures. Notwithstanding, further study is need to evaluate the fracture outcome in long-term follow-up.

The present findings must be interpreted in the context of a number of potential strengths and weaknesses. The data were obtained from a small sample size without placebo control and the study patients were Thai, among whom, genetic backgrounds, severity of disease and environmental living conditions are different from other populations. Thus care should be taken when extrapolating these results to other populations. Moreover, the follow-up period of the study was only 12 months, longer follow-up may be required to determine the rate of fractures. However, in our knowledge, this was the first study to demonstrate the efficacy of low dose intravenous Zol on BMD and BTMs in SSc patients with osteoporosis. It is likely that 4 mg of generic Zol annually will be more acceptable to SSc patients with osteoporosis due to similar efficacy with standard regimen. It may increase an adherence to long-term osteoporosis treatment with substantially decrease the cost of treatment, and potentially therefore increase access to treatment for a greater number of SSc patients.

In summary, single dose of 4 mg zoledronic acid was associated with a significantly increased in

lumbar spine BMD and sustained supppress bone formation and resorption markers in SSc patients with osteoporosis during a 12-month study period. Taken together with a favorable safty profile and well tolerated from the treatment, 4 mg of Zol administration annually could be used as the first line of treatment in SSc patients with osteoporosis in clinical practice.

What is known about this topic?

Osteoporosis is common in patients with systemic sclerosis [SSc]. Oral bisphosphonates is not recommended for osteoporosis treatment in SSc paitients due to increased risk of esophagitis.

What this study adds?

Administration of 4 mg intravenous zoledronic acid increased both lumbar spine and total hip BMD and suppress both bone formation and resorption markers with good safety profiles in SSc patients with osteoporosis

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Potential conflicts of interest

The authors declare no conflict of interest.

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