Original Article

Effect of 2 mg Versus 4 mg of Intravenous Zoledronic Acid on Bone Mineral Density at the Lumbar Spine in Indian Postmenopausal Women with Osteoporosis: A Double-blind Parallel-arm Randomized Controlled Trial

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ABSTRACT

Objective: The primary purpose was to compare the effect of 2 mg and 4 mg of intravenous zoledronic acid (ZA) on change in the lumbar spine (LS) bone mineral density (BMD) at the end of 1 year in postmenopausal women with osteoporosis. The secondary objectives were changes in BMD at the total hip and femoral neck, change in bone turnover markers (BTMs), and the incidence of new fractures. **Methods:** This was a double-blind, parallel-arm, randomized control trial with an allocation ratio of 1:1 done in 70 postmenopausal women with osteoporosis. **Findings:** The mean (±standard deviation) percentage increase in LS BMD at the end of 1 year was 4.86% ± 3.05% and 5.35% ± 3.73% in the 2 mg and 4 mg group, respectively. The dose of 2 mg ZA proved to be inferior to 4 mg with a noninferiority margin of 0.5%. There was no difference in BMD change at hip and BTMs between the two groups at the end of 1 year. Only one patient in 4 mg group developed two new vertebral fractures during a 12-month follow-up. Acute-phase reactions were the most common (43%) side-effects noted without any difference between the two groups ($P = 0.63$). **Conclusion:** This study failed to show the noninferiority of 2 mg ZA compared to 4 mg ZA for change in LS BMD at the end of 1 year.

KEYWORDS: *Bisphosphonates, fracture, neck of the femur, total hip, vertebral*

INTRODUCTION

Osteoporosis is a skeletal disease associated with the low bone mass and distortion of the bone tissue's microarchitecture.[1] As it is usually asymptomatic, it is considered a "silent disease" until the fractures occur. In nine industrialized countries (United States of America, Canada, five European countries, Japan, and Australia), country-specific osteoporosis prevalence at hip/spine ranges from 9% to 38% for women and 1%–8% for men.[2] It is estimated that 50 million people in India were either osteoporotic or osteopenic in 2013.[3] The majority of osteoporosis patients are postmenopausal women. Menopause is associated with an imbalance in the bone remodeling process, with resorption exceeding formation, resulting in osteoporosis.[4] The prevalence of osteoporosis among Indian postmenopausal women varies from 42.5% to 62% in different studies.[5]

Bisphosphonates are effective agents for the management of postmenopausal osteoporosis. Currently, zoledronic

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acid (ZA) is used in a dose of 5 mg intravenous (IV) infusion once a year.[4] This is based on the findings from HORIZON PFT (Health Outcomes and Reduced Incidence with ZA Once-Yearly Pivotal Fracture Trial), which showed that ZA 5 mg once in a year reduced both vertebral and nonvertebral fractures with improvement in bone mineral density (BMD) and bone metabolism markers as compared to placebo.[6] However, both 4 mg and 5 mg dose of ZA are used once in a year to treat postmenopausal osteoporosis in India, depending on the availability. Few studies have shown that lower doses of ZA (1 mg, 2 mg, and 2.5 mg) generate similar spine and hip BMD levels as with standard doses of ZA (4 mg and 5 mg) in postmenopausal patients with osteopenia.[7,8] However, none of the studies have used a lower dose of ZA to evaluate its effect on BMD in patients with postmenopausal osteoporosis. India is a resource-limited country, and most patients pay out of their pocket for treatment as health insurance coverage is minimal. This is also applicable to most of the countries in the world. It is a fundamental tenet of medicine to administer the least treatment necessary to produce the desired result. Such an approach is cost-effective and also is expected to have lesser side effects.[9]

Currently, there is a dearth of studies comparing the efficacy of either 4 mg or 5 mg ZA with lower doses in postmenopausal osteoporotic patients. ZA is available as a 4 mg dose in our hospital. Hence, this randomized control trial (RCT) was conducted to study the comparative efficacy of two different dosing regimens of IV ZA, i.e., 2 mg and 4 mg, on change in the lumbar spine (LS) BMD at the end of 1 year in postmenopausal women with osteoporosis.

Methods

This study was conducted in the Endocrinology department of an academic research institute in India from June 2017 to December 2018 and was a double-blind, parallel-arm RCT with an allocation ratio of 1:1. The Clinical Trials Registry-India (CTRI) registration (CTRI/2017/05/008696) for this study was done prospectively on May 20, 2017.

The primary objective was to compare the effect of 2 mg and 4 mg of IV ZA on change in LS BMD at the end of 1 year in postmenopausal women with osteoporosis. The secondary objectives were to study its effect on BMD change at the total hip (TH) and femoral neck (FN), bone turnover markers (BTMs), and the incidence of new fractures at 1 year. Osteoporosis was defined as a BMD T-score of − 2.5 or less at the LS (L1–L4), FN, or TH with/without fractures.[1]

The needed sample size was estimated by nMaster software considering a non-inferiority margin of 0.5%,[8] an alpha error of 2.5%, and an allocation ratio of 1:1. Taking standard deviation (SD) as 0.7%[8] and assuming a dropout rate of 10%, at least 35 patients per treatment group were required to give 80% power. The noninferiority margin of 0.5% was decided based on findings from the study by Grey *et al*., where the mean (95% confidence interval [CI]) increase in LS BMD in 5 mg IV ZA versus placebo was 3.6% (2.3%–4.9%) at 12 months in postmenopausal women with osteopenia.[8] As 25% of the lower margin of CI is 0.57% and 4 mg ZA was used instead of 5 mg ZA in the standard arm in our study, the noninferiority margin of 0.5% was considered for the sample size calculation. Similarly, a noninferiority margin of 0.7% as a change in LS BMD at 12 months was taken in a trial comparing 5 mg IV ZA and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis among adult patients.[10] Consecutive osteoporotic women aged between 50 and 80 years who were postmenopausal for at least 5 years were recruited to the study. Patients with the evidence of secondary osteoporosis, chronic kidney disease, chronic liver disease, chronic infection, cancer, low serum 25-OH Vitamin D level, and usage of medications known to affect the skeleton, including anti-osteoporosis drugs, for example, bisphosphonates, teriparatide, calcitonin, hormone replacement therapy were excluded from this study.

Patients were randomized to two arms after obtaining the Institute Ethics Committee approval. This study was performed in line with the principles of the Declaration of Helsinki. Randomization was done by block randomization with variable block sizes using standard software by an independent research scholar who was not attached to this study. The primary investigator did intervention allocation after obtaining written informed consent from the eligible participants. The allocation sequence was concealed in sequentially numbered, opaque, and sealed envelopes. This being a double-blind study, neither the patient nor the primary investigator was aware of the intervention being given to the patient. The ZA infusion was provided by the two independent nursing staff not attached to the study (one prepared the ZA solution, and the other administered it).

Patients in Group 1 and Group 2 received a single IV infusion of 2 mg and 4 mg ZA in 100 ml of normal saline over 30 min, respectively. A baseline electrocardiogram was done for all patients before the infusion of ZA in the Endocrinology ward. Patients were monitored for the postinfusion adverse effects. Patients were advised to report if they developed palpitations,

carpopedal spasms, oliguria, or any allergic reaction after infusion. In addition to ZA, all patients in both groups received oral daily calcium (1000 mg) and Vitamin D (500 IU/day).

At baseline, detailed history including age, smoking, alcohol intake, and years since menopause was taken. Physical examination, including anthropometric evaluation, was done in the endocrinology outpatient department. Baseline laboratory investigations included fasting serum calcium along with albumin, phosphorus, alkaline phosphatase (ALP), creatinine, 25(OH) D, plasma intact parathyroid hormone (iPTH), and BTMs.[11] These investigations were repeated at 6 and 12 months except for serum 25(OH) D and plasma iPTH, which were repeated only at 12 months. Venous blood samples were collected in the early morning after an overnight fast. All parameters except BTMs were processed on the same day. For BTMs, samples were centrifuged, and plasma was separated and stored at −80°C. Stored plasma samples were batch analyzed at the end of the study.

Biochemical parameters, including calcium, phosphorus, albumin, ALP, and creatinine, were measured using an AU5800 analyzer (Beckman Coulter, CA, USA). Both serum 25(OH) D and plasma iPTH were measured by chemiluminometric technology (ADVIA Centaur XP Immunoassay System, Siemens Healthcare Global, USA). The range of the detection of serum 25(OH) D was 4.2–150 ng/ml (10.5–375 nmol/L). The within-run and total coefficient of variation (CV) of this assay were 7.0% and 11.1%, respectively. The range of the detection of plasma iPTH was 4.6–2200 pg/ml (0.488–233 pmol/L). The within-run and total CV of this assay were 8.0% and 10.0%, respectively.

The BTMs like plasma C-terminal telopeptide of type I collagen (β-CTX) and procollagen type I N-terminal propeptide (P1NP) were measured by electrochemiluminescence immunoassay (Cobas e 411 immunoanalyzer, Roche diagnostics GmbH, Mannheim, Germany). The range of detection of β-CTX was 0.010-6.00 ng/ml. The intra-assay and inter-assay CV for its values between 0.03 and 0.5 ng/ml were <10% and for values between 0.5 and 5 ng/ml were <3% and <6%, respectively. The range of detection of P1NP was 5–1200 ng/ml. The intra-assay and inter-assay CV for its values <50 ng/ml were <5% and <7%, respectively, and for values between 50 and 500 ng/ml were <4% and <5%, respectively.

Patients were screened for prevalent vertebral fracture (VF) by x-rays of the thoracic and LS. Lateral and AP radiographs of the thoracic and LS (T4–L4) were obtained using the same X-ray machine at 6 months, 12 months, or if the patient complained of back pain suggestive of VF. Radiographs were assessed using Genant grading scale[12] by the same radiologist at all-time points: Grade 0: Normal un-fractured vertebrae; grade 1: 20%–25% reduction in any (anterior, middle, and/or posterior) height; grade 2: 25%–40% reduction in any height and grade 3: If the reduction was >40%. Patients were considered to have an incident VF if there was an increase of at least one grade in a vertebra with grade 0, 1, or 2 fracture.

The BMD (in g/cm^2) of LS (L1-L4), nondominant FN, and TH were measured at baseline, 6 months, and at 12 months using dual-energy X-ray absorptiometry (DXA) (Discovery Wi System, Hologic, Bedford, MA, USA). An expert radiologist reviewed the x-rays of the thoracic and LS to ensure that at least two contiguous vertebrae in the region L1–L4 were normal or mild deformity as per Genant grading scale before DXA scan.[12] An experienced technician performed BMD measurements at all time-points. The same technician carried out measures for the entire study period. The quality control for the machine was performed with daily phantom scans for LS. The data from calibration and phantom scans were plotted and reviewed. The least significant change (LSC) was calculated for the technologist. Our technologist's *in vivo* precision assessment was done by measuring 15 patients three times in accordance with the International Society for Clinical Densitometry (ISCD) guidelines.[13] After each scan, the patient was repositioned. These values were entered in the online LSC calculator, and LSC was determined at the 95% CI. The LSC for LS, FN, and TH were 0.01, 0.035, and 0.012 g/cm^2, respectively, in our study.

The study was analyzed following perprotocol analysis. Continuous variables were represented as mean ± SD or median with inter-quartile range, depending on the variable's distribution. Categorical variables were expressed as a percentage and were analyzed using Chi-squared test. The normality of the data was assessed using appropriate tests. Paired *t*-test and Wilcoxon signed-rank test were used for intra-group comparison (baseline and 12 months) for parametric and nonparametric data. Independent Student's *t*-test and Mann–Whitney U test were done to compare two independent groups based on the normality. $P < 0.05$ was considered significant. Statistical analysis was performed using the Statistical Package for the Social Sciences version 19 (IBM Corp., Armonk, NY, USA). The noninferiority analysis was performed using Number Cruncher Statistical Software version 12 (NCSS, LLC, Kaysville, Utah, USA).

Results

A total of 70 patients (35 in each group) were recruited in this study [Figure 1]. At the end of 12 months, 64 patients (31 in group 1 and 33 in group 2) completed the study. Four from Group 1 and two from Group 2 were lost to follow-up. Out of 70 patients, 67 (96%) had osteoporosis at LS, whereas osteoporosis at FN and TH was present in 21 (30%) and 14 (20%) patients, respectively. There was no difference between the two groups with respect to the baseline characteristics [Table 1]. However, TH-BMD tended (P = 0.06) to be higher in patients receiving 2 mg ZA. None of our patients had a history of smoking or alcohol intake. Euthyroidism was ensured for all hypothyroid patients during the study period.

The BMD at both LS and FN increased significantly at 12 months from baseline in both groups [Supplemental Table 1]. However, the change in FN BMD and TH BMD were less than LSC in our study. The mean percentage increase in BMD at LS in the 2 mg group from baseline to the end of 12 months was 4.86% ± 3.06%, whereas for the 4 mg group was 5.35% ± 3.73%, as shown in Table 2. The mean difference between two groups was 0.49% (95% CI: −1.2% to + 2.2%). This result suggests that the mean difference in LS BMD increments between two groups at 1 year is not >2.2%. As the 95% upper CI limit was above the inferiority margin of 0.5%, the null hypothesis of inferiority was accepted, and the dose of 2 mg ZA proved to be inferior to 4 mg (P = 0.50). Most of the LS-BMD improvement occurred in the first 6 months after the treatment [Figure 2a].

Both β-CTX and P1NP demonstrated a reduction at 12 months from the baseline in both groups. The nadir level of both markers was recorded at 6-month, following a mild rise in the levels [Figure 2b and c]. However, both markers were >50% below their baseline values at 12 months, demonstrating the durability of response without differences in both groups. Fasting serum calcium profile, renal function test, serum 25(OH) D, and plasma iPTH were within the normal range throughout the study in both groups.

Two patients in Group 1 and five patients in Group 2 had nine VFs at baseline. Out of nine VFs, one was grade 1, five were grade 2, and three were grade 3. One patient in Group 2 developed two new VFs (grade 1 fracture in T11 and grade 2 fracture in L2 vertebra) at 12-month follow-up. There was no

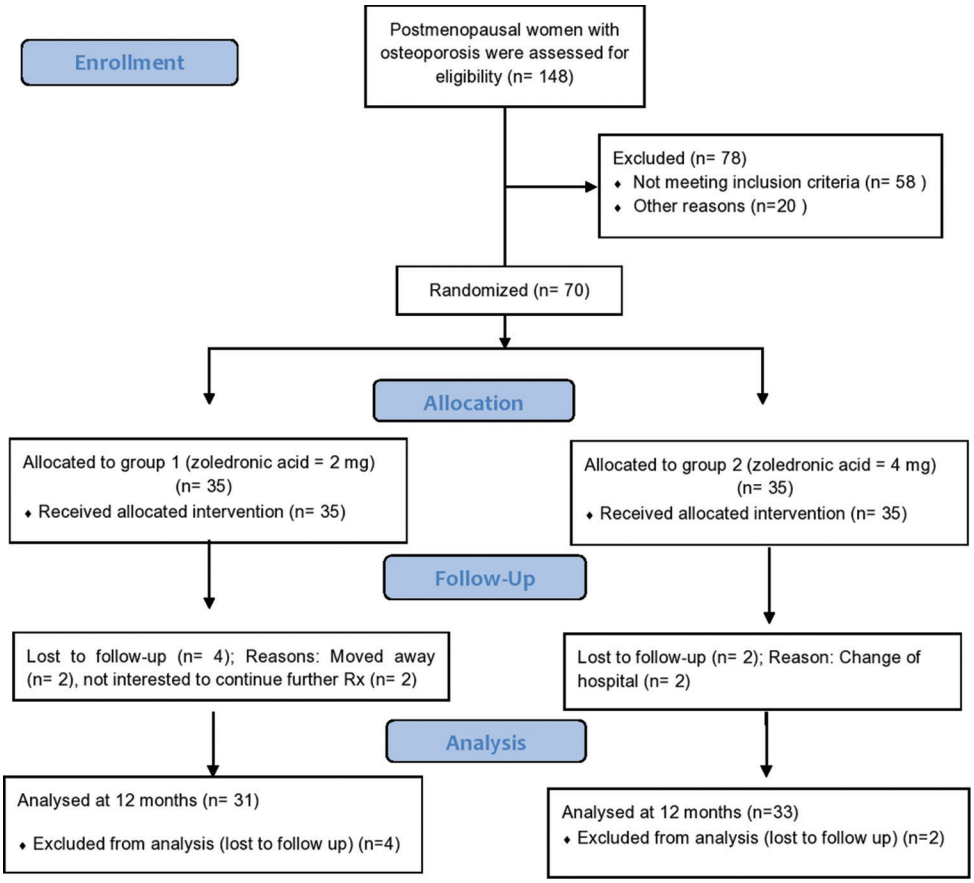

Figure 1: CONSORT flow diagram for the study

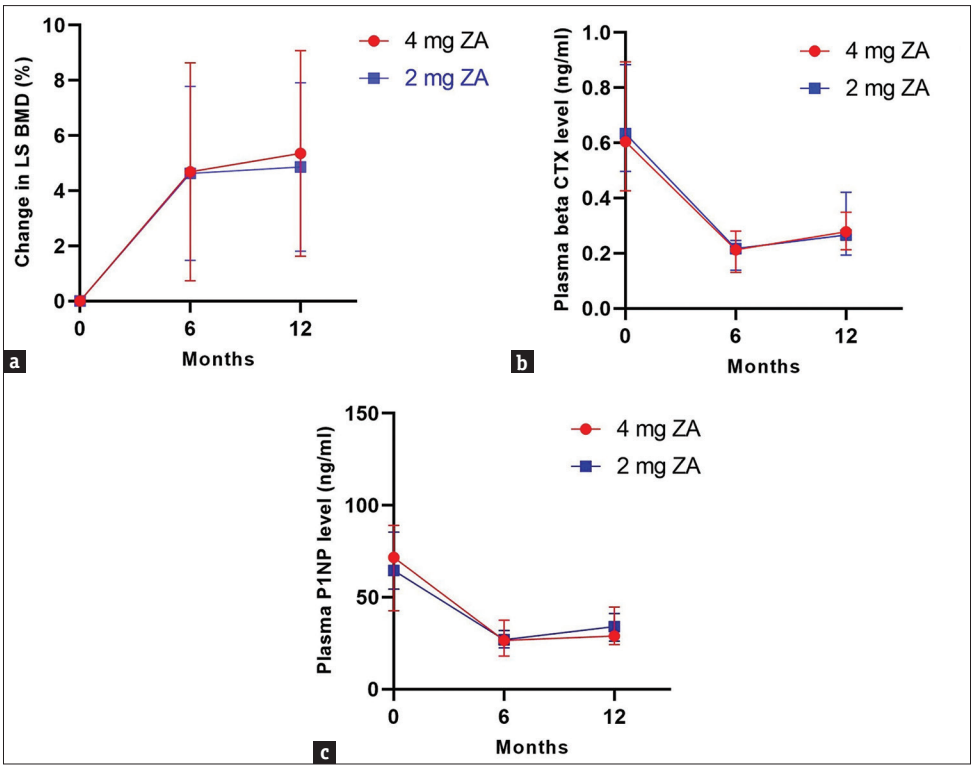

Figure 2: (a) Effect of various doses of zoledronic acid on the percentage change in lumbar spine bone mineral density over 1 year (data is depicted as mean ± standard deviation). (b) Effect of various doses of zoledronic acid on plasma C-terminal telopeptide of type I collagen (β-CTX) over 1 year (data is depicted as median with inter-quartile range). (c) Effect of various doses of zoledronic acid on plasma procollagen type I N-terminal propeptide (P1NP) over 1 year (data is depicted as median with inter-quartile range). The plasma β-CTX and P1NP were lower at 6 months and 12 months compared to baseline in both groups ($P < 0.001$)

Table 1: Baseline characteristics of the study groups

Parameters*	2 mg group (*n*=35)	4 mg group (*n*=35)	*P*
Age (years)	58 (55-63)	58 (56-64)	0.74
Years since menopause	12 (7-15)	15 (7-17)	0.37
DM, *n* (%)	9 (25.7)	9 (25.7)	1.00
HTN, *n* (%)	15 (42.9)	10 (28.6)	0.21
Hypothyroidism, *n* (%)	10 (28.6)	10 (28.6)	1.00
BMI (kg/m^2)	24.6 (22.1-26.6)	22 (19.2-26.5)	0.12
Serum creatinine (mg/dl)	0.8 (0.7-0.9)	0.88 (0.8-0.97)	0.07
Serum calcium (mg/dl)	9.05±0.59	9.14±0.54	0.51
Serum phosphorus (mg/dl)	3.64±0.53	3.73±0.47	0.44
Serum alkaline phosphatase (IU/L)	234±56.94	239.1±69.79	0.73
Serum 25(OH) D (ng/ml)	24.8 (20.1-34)	27.73 (20.99-38.06)	0.56
Plasma iPTH (pg/ml)	47.76±19.5	45.56±16.44	0.61
Plasma β-CTX (ng/ml)	0.663±0.277	0.68±0.342	0.82
Plasma P1NP (ng/ml)	66.15 (54.55-84.87)	71.65 (42.9-87.66)	0.95
LS-BMD (g/cm^2)	0.707±0.060	0.705±0.067	0.87
FN-BMD (g/cm^2)	0.6 (0.58-0.67)	0.6 (0.56-0.66)	0.29
TH-BMD (g/cm^2)	0.736±0.069	0.700±0.089	0.06

*The continuous variables are presented as mean±SD or median with IQR. SD=Standard deviation, BMI=Body mass index, DM=Diabetes mellitus, HTN=Hypertension, 25(OH) D=25-hydroxy Vitamin D, iPTH=Intact parathyroid hormone, β-CTX=C-terminal telopeptide of type I collagen, P1NP=Procollagen type I N-terminal propeptide, BMD=Bone mineral density, LS-BMD=Lumbar spine-BMD, FN-BMD=Femoral neck-BMD, TH-BMD=Total hip-BMD, IQR=Inter-quartile range

deterioration (i.e., increase in grading) of any prevalent fracture (grade 1 or 2) during the study period in either group.

Acute-phase reactions (APR) were the most common adverse effect noted in our study participants in 3 days of the drug administration. A total of 30 (43%) patients

Table 2: Comparison of percentage changes in various parameters at 12 months from baseline

Parameters*	2 mg (*n*=31)	4 mg (*n*=33)	*P*
Percentage change in LS-BMD	4.86±3.05	5.35±3.73	0.50†
Percentage change in FN-BMD	2.09 (−0.81−2.90)	1.17 (−0.69−3.70)	0.90
Percentage change in TH-BMD	1.55 (−1.08−3.71)	1.43 (−1.27−3.76)	0.73
Percentage change in plasma β-CTX	56.49 (37.05-66.5)	56.80 (41.9-67.9)	0.78
Percentage change in plasma P1NP	51.14 (29.02-57.14)	51.73 (34.07-62.98)	0.76

*The data are presented as mean±SD or median with IQR, †*P*-value of the noninferiority test. BMD=Bone mineral density, LS-BMD=Lumbar spine-BMD, FN-BMD=Femoral neck-BMD, TH-BMD=Total hip-BMD, β-CTX=C-terminal telopeptide of type I collagen, P1NP=Procollagen type I N-terminal propeptide, SD=Standard deviation, IQR=Inter-quartile range

developed APR in our study [Supplemental Table 2]. Pyrexia was seen in 24%, whereas flu-like illness was seen in 13% of the participants. Patients developing APR were treated symptomatically with tablet paracetamol. There was no difference in the occurrence of adverse events between the two groups (P = 0.63). None of our patients developed any significant adverse effects such as deterioration in renal function, atrial fibrillation, symptomatic hypocalcemia, or ocular inflammation.

Discussion

Our study was conducted to elucidate the effects of different doses of ZA in postmenopausal women with osteoporosis. The 2 mg ZA proved to be inferior to the 4 mg with respect to LS BMD change at 12 months by noninferiority analysis. In 2002, Reid *et al*. compared the effect of various doses of ZA ranging from 1 mg to 4 mg/year on BMD in postmenopausal women with osteopenia (T-score <−2.0).[7] At the end of 12 months, the increase in LS-BMD ranged from 4.3%–5.1% in all ZA groups compared to placebo. In 2012, Grey *et al*. demonstrated the improvement of 4% and 3.6% in LS-BMD at 12 months with 2.5 mg and 5 mg ZA, respectively, compared with placebo in postmenopausal women with osteopenia (T-score between-1.0 to-2.5).[8] In our study, the mean increase in LS-BMD was 4.86% in 2 mg group compared to 5.35% in 4 mg group at the end of the 12 months. The improvement in both groups was highly significant when compared to baseline. However, when the analysis was performed using a noninferiority margin of 0.5%, 2 mg proved to be inferior compared to 4 mg in improving LS-BMD at 12 months. Our study reinforces the use of a conventional dose of ZA (4 mg) instead of a low dose (2 mg) in postmenopausal osteoporotic patients. As 2 mg ZA was inferior to 4 mg ZA, we could not continue 2 mg arm beyond 12 months due to ethical reasons.

In our study, the rise in BMD at LS in both groups was more than the change in BMD at FN and TH. This can be explained by the baseline difference in osteoporosis at various sites in our subjects. It is a known fact that the rise in BMD is larger in patients with lower baseline BMD.[14] Only 21 of our patients had osteoporosis at FN, and 14 had osteoporosis at TH, whereas osteoporosis at LS was present in 67 patients. As almost all of our patients had osteoporosis at LS, the BMD improvement was more significant at LS than hip. Trabecular to the cortical bone ratio in vertebral body is 75:25, whereas, in FN, it is around 30:70.[15] The trabecular bone is the more metabolically active compartment of the bone, and cortical bone with a low surface-to-volume ratio undergoes slower remodeling than the trabecular bone.[16] This may be another reason why the BMD change at the spine responded better than that of the hip.

The BTMs decreased significantly in both groups in this study. Various studies have shown reductions ranging from 50% to 60% in CTX and P1NP levels at 12 months.[6-8] Reid *et al*., in their study on variable doses of ZA, demonstrated a 49%–52% reduction in CTX levels at 12 months.[7] There was evidence of dose-dependency in the effect of ZA on both β-CTX and P1NP in the study by Grey *et al*.[8] Serum β-CTX decreased by 68% in 2.5 mg and 73% in the 5 mg ZA group compared to placebo.[8] Similarly, serum P1NP showed a reduction of 58% in 2.5 mg and 64% in the 5 mg ZA group compared to placebo.[8] In HORIZON PFT, CTX decreased by 59%, and P1NP reduced by 58% at the end of 12 months.[6] Although there was a mild increase in BTMs in both groups from 6 to 12 months in our study, the markers were still >50% below their baseline values at 12 months [Figure 2b and c].

APR was noted in 30 (43%) of our participants. The incidence of adverse effects in our study is comparable to that seen in other studies.[6,7,9,17,18] APR is characterized by transient fever with myalgias, arthralgias, headaches, and flu-like symptoms. This is due to pro-inflammatory cytokine production by peripheral blood γδ T-cells.[9] Pretreatment with histamine receptor antagonists or antipyretics can reduce the incidence and severity of symptoms among susceptible patients. Occasionally, corticosteroids are of benefit. All of our patients with APR responded to antipyretics.

The major strength of our study is its double-blind, randomized control, noninferiority design. Ours is also the first study to analyze the effects of variable doses of ZA in postmenopausal osteoporotic patients. However, it also has few limitations. We measured BTMs 6 monthly due to the limited availability of resources. More frequent measurement of these parameters could have elucidated the trend in a better way as BTMs reach nadir between 1 and 3 months after ZA administration.[11] Short duration of follow-up is another limitation of this study as 1 year is not adequate enough to comment on the long-term trend of BMD and fracture outcomes. As the study was done in Indian postmenopausal women, the findings may not be applicable to other population.

In conclusion, this study failed to show the noninferiority of 2 mg ZA compared to 4 mg ZA with respect to change in LS BMD at the end of 1 year. These findings reinforce the use of a conventional dose of ZA (4 mg) in postmenopausal osteoporotic patients.

Authors' Contribution

All authors contributed to the study conception and design. The data collection, analysis and interpretation were performed by (Harsh Durgia), (Sadishkumar Kamalanathan), (Jayaprakash Sahoo) and (Sonali Sarkar). All authors revised it critically for important intellectual content and approved the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

References

1. Kanis JA, Glüer CC. An update on the diagnosis and assessment of osteoporosis with densitometry. Committee of Scientific Advisors, International Osteoporosis Foundation. Osteoporos Int 2000;11:192-202.
2. Wade SW, Strader C, Fitzpatrick LA, Anthony MS, O'Malley CD. Estimating prevalence of osteoporosis: Examples from industrialized countries. Arch Osteoporos 2014;9:182.
3. Mithal A, Bansal B, Kyer CS, Ebeling P. The asia-pacific regional audit-epidemiology, costs, and burden of osteoporosis in India 2013: A report of International Osteoporosis Foundation. Indian J Endocrinol Metab 2014;18:449-54.
4. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological management of osteoporosis in postmenopausal women: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2019;104:1595-622.
5. Marwaha RK, Tandon N, Garg MK, Kanwar R, Narang A, Sastry A, *et al*. Bone health in healthy Indian population aged 50 years and above. Osteoporos Int 2011;22:2829-36.
6. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, *et al*. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356:1809-22.
7. Reid IR, Brown JP, Burckhardt P, Horowitz Z, Richardson P, Trechsel U, *et al*. Intravenous zoledronic acid in postmenopausal women with low bone mineral density. N Engl J Med 2002;346:653-61.
8. Grey A, Bolland M, Wong S, Horne A, Gamble G, Reid IR. Low-dose zoledronate in osteopenic postmenopausal women: A randomized controlled trial. J Clin Endocrinol Metab 2012;97:286-92.
9. Drake MT, Clarke BL, Khosla S. Bisphosphonates: Mechanism of action and role in clinical practice. Mayo Clin Proc 2008;83:1032-45.
10. Reid DM, Devogelaer JP, Saag K, Roux C, Lau CS, Reginster JY, *et al*. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): A multicentre, double-blind, double-dummy, randomised controlled trial. Lancet 2009;373:1253-63.
11. Szulc P, Naylor K, Hoyle NR, Eastell R, Leary ET; National Bone Health Alliance Bone Turnover Marker Project. Use of CTX-I and PINP as bone turnover markers: National Bone Health Alliance recommendations to standardize sample handling and patient preparation to reduce pre-analytical variability. Osteoporos Int 2017;28:2541-56.
12. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993;8:1137-48.
13. Lewiecki EM, Binkley N, Morgan SL, Shuhart CR, Camargos BM, Carey JJ, *et al*. Best practices for dual-energy X-ray absorptiometry measurement and reporting: International Society for Clinical Densitometry Guidance. J Clin Densitom 2016;19:127-40.
14. Eastell R, Black DM, Boonen S, Adami S, Felsenberg D, Lippuner K, *et al*. Effect of once-yearly zoledronic acid five milligrams on fracture risk and change in femoral neck bone mineral density. J Clin Endocrinol Metab 2009;94:3215-25.
15. Hunter DJ, Sambrook PN. Bone loss. Epidemiology of bone loss. Arthritis Res 2000;2:441-5.
16. Pazianas M, van der Geest S, Miller P. Bisphosphonates and bone quality. Bonekey Rep 2014;3:529.
17. Reid IR, Gamble GD, Mesenbrink P, Lakatos P, Black DM. Characterization of and risk factors for the acute-phase response after zoledronic acid. J Clin Endocrinol Metab 2010;95:4380-7.
18. Okimoto N, Sakai A, Yoshioka T, Kobayashi T, Asano K, Akahoshi S, *et al*. Efficacy of non-steroidal anti-inflammatory drugs on zoledronic acid-induced acute-phase reactions: Randomized, open-label, Japanese OZ study. J Bone Miner Metab 2020;38:230-9.