Original Article

Effect of Zoledronic Acid in Hepatic Osteodystrophy: A Double-Blinded Placebo-Controlled Trial

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Abstract

Purpose: Literature on the treatment of pre-transplant hepatic osteodystrophy (HOD) is limited. The general treatment measures and their timing are currently adopted from the literature on postmenopausal osteoporosis. Therefore, we conducted this randomized study to investigate the effect of zoledronic acid (ZA) on HOD. **Methods:** We randomized 36 male patients with cirrhosis (Child–Pugh class A and B) into 19 to the ZA arm and 17 to the placebo arm, respectively. Patients in the ZA arm received a single infusion of 4 mg ZA dissolved in 100 mL of normal saline at baseline, while patients in the placebo arm received a similar infusion of normal saline at baseline. The primary outcome of the study was the change in lumbar spine bone mineral density (LS-BMD) at 12 months. **Results:** Of 36 patients, 28 completed the study (15 in the ZA arm and 13 in the placebo arm). The mean increase in LS-BMD (g/cm^2) in the ZA and placebo arms was 5.11% (3.50) and 0.72% (4.63) [P = 0.008], respectively. The trabecular bone score (TBS) did not improve significantly in either arm. The incidence of vertebral fractures (VFs) was similar in both arms. There was a significant decrease in plasma beta-C-terminal telopeptide (β-CTX) levels in the ZA arm compared to the placebo arm, while the change in plasma levels of procollagen 1 intact N-terminal propeptide (P1NP) was similar in both arms. Six patients (31.6%) in the ZA arm experienced adverse reactions such as fever and myalgia. **Conclusion:** ZA improved LS-BMD in male patients with HOD by decreasing bone resorption. However, it may not improve trabecular microarchitecture or prevent morphometric VFs in this population.

Keywords: Bone mineral density, bone turnover markers, hepatic osteodystrophy, trabecular bone score, zoledronic acid

Introduction

Metabolic bone diseases are a common consequence of various liver diseases. Bone metabolism changes in chronic liver disease are defined as hepatic osteodystrophy (HOD).[1] HOD is a condition of low bone mass that includes osteopenia, osteoporosis and rarely osteomalacia. The prevalence of osteoporosis, osteopenia and fractures in patients with HOD varies from 3–48%, 20–68% and 5.3–23.7%, respectively. Lifestyle factors (alcohol, smoking and malnutrition), genetic factors (polymorphisms in vitamin D receptor and insulin-like growth factor 1 (IGF1)), vitamin D and K deficiency, hyperbilirubinaemia, testosterone deficiency, IGF1 deficiency and drugs are the most important factors involved in the pathogenesis of HOD. There is deterioration in both cortical and trabecular microarchitecture in HOD, increasing the risk of fracture in these patients.[2] The gold standard for diagnosing HOD is measuring bone mineral density (BMD) at the lumbar spine (LS) and hip using dual-energy X-ray absorptiometry (DXA). However, before diagnosing HOD, other secondary causes of osteoporosis must be ruled out.[1]

Currently, there is yet to be a clear consensus on routine screening and management of HOD. Treatment recommendations were taken from the literature on postmenopausal osteoporosis.[3] In addition, the effect of zoledronic acid (ZA) on pre-transplant HOD has yet to be evaluated in a study. Therefore, we planned

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to test the efficacy of ZA in HOD using a randomized controlled trial (RCT) design.

Materials and Methods

This study was initiated following approval by the Institute Ethics Committee (JIP/IEC/2017/0171) and registration with the Clinical Trials Registry–India (CTRI) (CTRI/2018/02/011761). We conducted this study from August 2017 to May 2019 at the departments of Endocrinology and Medical Gastroenterology of a tertiary care centre in India. Our study was a randomized, double-blind, placebo-controlled trial with an allocation ratio of 1:1.

We calculated the sample size based on data from the first year of the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) trial, an RCT evaluating ZA treatment in postmenopausal osteoporosis.[4] Power was set at 80% and alpha at 5%. Hypothesis testing for two means was used to calculate the sample size. To demonstrate that the treatment effect of ZA was superior to placebo using LS-BMD) as the primary endpoint, the number needed was 20 per arm. Assuming a 10% dropout rate, the sample size was 22 per arm. However, due to time constraints, we could not recruit the calculated number of patients.

Patient selection and methods

The study was conducted in male cirrhotic patients (Child class A and B) aged 18 to 70 years with an LS Z-score of ≤-2. Patients with chronic kidney disease, primary hyperparathyroidism, thyrotoxicosis, Cushing's syndrome, human immunodeficiency virus (HIV) infection, malignancies (other than hepatocellular carcinoma) and current steroid use were excluded. The aetiologies of cirrhosis were alcohol alone in 15 participants, alcohol and hepatitis B in eight, cryptogenic in 10, hepatitis B in two and hepatitis C in one patient each. Of the 36 patients, 14 had Child class A cirrhosis, while the remaining 22 had Child class B disease. At the start of the study, there was no difference between the two arms in any of the parameters.

Eligible patients were randomized using random block sizes. The allocation number was generated by standard random number generation software. An independent researcher not involved in the study generated the random allocation sequence. The allocation sequence was concealed in sequentially numbered, opaque, sealed and stapled envelopes. The sealed envelope was given to the nursing staff, who opened the envelope and prepared the infusion in a separate room. An independent nurse not involved in the study administered the infusion. Both the patient and the investigator were blind to the intervention performed.

Medical history including age, history of fracture(s), comorbidities such as diabetes, habits (such as smoking, tobacco chewing or alcoholism) and drug history was recorded at baseline. Clinical examination, including anthropometric evaluation, was performed. The study patients were randomized to one of the two arms. Patients in the intervention arm received a single intravenous infusion of 4 mg of ZA (Zolebenz, Cadma Biotech Ltd.) in 100 mL of normal saline over 30 minutes at baseline, while patients in the placebo arm received a similar intravenous infusion of 100 mL of normal saline over 30 minutes. Patients in both arms received oral calcium (1000 mg) and oral cholecalciferol (500 IU/day) daily throughout the study period. In this study, vitamin D deficiency was defined as a serum level of 25-hydroxyvitamin D [25(OH)D] less than 15 ng/mL.[5,6] Vitamin D-deficient patients received 600,000 IU cholecalciferol (Arachitol, Abbott India Ltd.) intramuscularly 2 months before the start of the study. Patients were monitored for post-infusion side effects. Those who developed flu-like symptoms were treated with acetaminophen tablets. In addition, patients found to be vitamin D-deficient after 6 months received corrective and maintenance therapy with cholecalciferol.

BMD

LS-BMD (L1–L4), femoral neck BMD (FN-BMD) and total hip BMD (TH-BMD) (g/cm^2) were measured at baseline, 6 months and 12 months using a Hologic DXA (Discovery Wi). The same technician performed the BMD measurements throughout the study period. Quality control for the machine was conducted with daily phantom scans for LS. Calibration and phantom scan data were recorded and verified. The least significant change (LSC) for LS, FN and TH was 0.01, 0.035 and 0.012 g/cm^2, respectively. Trabecular bone score (TBS) was measured from the lumbar spine DXA (LS DXA) images using the TBS iNsight software installed in our bone densitometer.

Radiographs

Patient eligibility was assessed using thoracic and LS radiographs. The radiographs were reviewed by an experienced radiologist to ensure that at least two adjacent vertebrae in the L1–L4 region were normal or had only mild deformity according to the Genant grading scale.[7] Lateral and anteroposterior radiographs of the thoracic and LS (T4–L5) were obtained using the same X-ray machine at 6 and 12 months, or when the patient developed back pain indicative of a vertebral fracture (VF). The same radiologist reviewed the radiographs at all time points. Documenting the deterioration of pre-existing fractures required an increase of at least one grade on the Genant grading scale. The spinal fracture index (SFI) was calculated by dividing the sum of the grades of each vertebra by the total number of vertebrae assessed.

Laboratory parameters

Baseline laboratory parameters included fasting serum calcium, serum albumin, serum phosphorus, serum testosterone, plasma intact parathyroid hormone (iPTH), serum 25(OH)D, liver function tests, prothrombin time (international normalised ratio) PT (INR) and serum creatinine. These parameters were measured at baseline, 6 months and 12 months, except for serum testosterone, liver function tests, PT (INR) and serum creatinine, which were only measured at baseline and 12 months. Plasma bone turnover markers (BTMs) such as

beta-C-terminal telopeptide (β-CTX), a bone resorption marker and procollagen 1 intact N-terminal propeptide (P1NP), a bone formation marker, were measured at baseline, 6 months and 12 months.

Venous blood samples were taken early in the morning after an overnight fast. Blood was collected in both plain and dipotassium ethylenediaminetetraacetic acid (EDTA) tubes. Blood samples collected in plain tubes were allowed to clot for 30 minutes and then centrifuged at 2500 rpm for 10 minutes at 4°C. All parameters except BTMs were measured on the same day. The blood samples were centrifuged and the plasma separated to be stored at -80˚C till the end of the study for measuring BTMs.

Plasma iPTH was measured by a 2-site sandwich immunoassay using direct chemiluminometric technology (ADVIA Centaur XP PTH). Serum 25(OH)D was measured using the ADVIA Centaur Vit D Assay, an 18-minute, single-run, competitive antibody immunoassay. Plasma β-CTX and P1NP were measured by electrochemiluminescence immunoassay (ECLIA) on a Cobas e 411 immunoanalyzer (Roche Diagnostics GmbH, Mannheim, Germany).

Statistical analysis

Data analysis was performed using per-protocol analysis. Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) depending on the distribution of the variable. Categorical variables were expressed as percentages and analysed using the Chi-square test (χ^2). The normality of the data was assessed using the Shapiro–Wilk test. To analyse the trend of changes over 12 months, repeated-measures analysis of variance (ANOVA) and Friedman's test were used for parametric and non-parametric data, respectively. Paired *t*-test and Wilcoxon signed-rank test were used for within-group comparison (baseline, 6 months and 12 months) for parametric and non-parametric data, respectively. Independent Student's *t*-test and Mann–Whitney U-test were performed to compare two independent groups based on the normality of data. A *P* value of <0.05 was considered significant. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 19.0.

Results

Study outline

A total of 36 patients (19 in the ZA arm and 17 in the placebo arm) were enrolled in this study [Figure 1]. At the end of the 12-month follow-up, 28 patients (15 in the ZA arm and 13 in the placebo arm) completed the study. Eight patients, four from each arm, did not complete the study. Seven patients were lost to follow-up. One patient underwent liver transplantation during the study.

Baseline characteristics

The mean age of our patients was 47 ± 9 years. There was no significant difference between the two arms at baseline [Table 1].

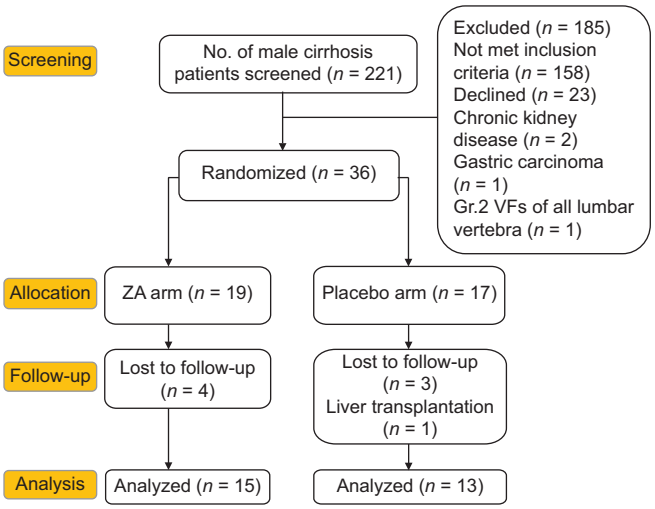

Figure 1: Consort diagram

Table 1: Baseline characteristics

Study parameter		ZA arm (*n*=19)	Placebo arm (*n*=17)
Age (years)*		47 (11)	46 (8)
Height (cm)**		162 (155-166)	162 (160-166)
BMI (kg/m²)*		22.6 (5.08)	20.1 (2.60)
Aetiology	Alcoholic	11	12
	Others	8	5
Child–Pugh class	Child A	9	5
	Child B	10	12
eGFR (ml/min)*		91.3 (16.3)	94.2 (14.5)
Calcium (mg/dl)*		9.39 (0.55)	9.23 (0.51)
Phosphate (mg/dl)*		3.40 (0.75)	3.50 (0.61)
Intact PTH (pg/ml)**		31.9 (19.2-53.6)	30.9 (16.9-51.0)
25(OH)D (ng/ml)**		17.4 (7.95-24.4)	15.1 (11.1-25.2)
Serum testosterone (ng/dl)*		424 (196)	340 (189)
LS-BMD	g/cm²*	0.763 (0.049)	0.746 (0.067)
	Z-score*	-2.684 (0.454)	-2.847 (0.605)
FN-BMD	g/cm²**	0.711 (0.595-0.758)	0.649 (0.593-0.694)
	Z-score**	-0.9 (-1.6 - -0.6)	-1.5 (-1.75 - -0.85)
TH-BMD	g/cm²*	0.796 (0.092)	0.762 (0.094)
	Z-score**	-1.2 (-1.9 - -0.8)	-1.7 (-1.95 - -1.25)
TBS*		1.28 (0.08)	1.31 (0.06)
β-CTX (ng/ml)*		0.589 (0.317)	0.499 (0.135)
P1NP (ng/ml)*		139 (89.4)	95.7 (34.5)
ALP (IU/L)**		259 (138-319)	240 (175-365)
SFI**		0.107 (0.036-0.143)	0.036 (0.036-0.232)

* mean±SD; ** median (IQR). LS-BMD – lumbar spine bone mineral density; FN-BMD – femoral neck bone mineral density; TH-BMD – total hip bone mineral density; TBS – trabecular bone score; β-CTX – beta-C-terminal telopeptide; P1NP – procollagen 1 intact N-terminal propeptide; ALP – alkaline phosphatase; SFI – spinal fracture index

Changes in BMD

LS-BMD increased significantly from baseline at 6 months and 12 months in the ZA arm ($P < 0.001$, Table 2). The mean percentage increase in LS-BMD in the ZA arm was 4.37 and 5.11 at 6 months and 12 months, respectively [Figure 2]. Most

Table 2: Trend of changes in various parameters in the ZA arm

Parameter		0 m	6 m	12 m	*P* (0-6-12)	*P* (0-12)	*P* (0-6)	*P* (6-12)
LS-BMD	g/cm²*	0.778 (0.043)	0.812 (0.048)	0.817 (0.045)	<0.001	<0.001	<0.001	1.00
	Z-score**	-2.5 (-2.7 - -2.3)	-2.1 (-2.4 - -1.8)	-2 (-2.4 - -1.8)	<0.001	0.001	0.001	0.693
FN-BMD	g/cm²*	0.714 (0.108)	0.720 (0.106)	0.726 (0.117)	0.303			
	Z-score*	-0.907 (0.848)	-0.847 (0.781)	-0.8 (0.888)	0.199			
TH-BMD	g/cm²**	0.838 (0.769-0.872)	0.853 (0.743-0.875)	0.847 (0.743-0.879)	0.034	0.099	0.164	0.172
	Z-score*	-1.127 (0.616)	-1.087 (0.587)	-1.027 (0.605)	0.058			
TBS**		1.27 (1.22-1.33)	1.30 (1.24-1.37)	1.29 (1.23-1.35)	0.344			
β-CTX (ng/ml)**		0.601 (0.430-0.905)	0.231 (0.172-0.280)	0.254 (0.161-0.373)	<0.001	0.005	0.005	0.281
P1NP (ng/ml)**		144 (87.0-225)	63.7 (42.8-87.0)	61.1 (42.2-81.4)	0.017	0.006	0.017	0.394
SFI*		0.099 (0.083)	0.153 (0.093)	0.202 (0.112)	0.001	0.003	0.012	0.005

*mean±SD; **median (IQR). LS-BMD – lumbar spine bone mineral density; FN-BMD – femoral neck bone mineral density; TH-BMD – total hip bone mineral density; TBS – trabecular bone score; β-CTX – beta-C-terminal telopeptide; P1NP – procollagen 1 intact N-terminal propeptide; SFI – spinal fracture index

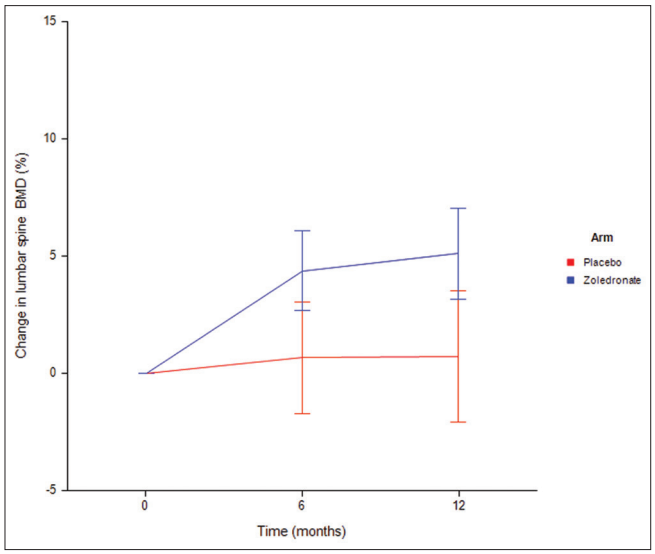

Figure 2: Effect of ZA vs placebo on LS-BMD in male patients with HOD. Data are the mean percentage change over 1 year (95% CI). The percentage change in LS-BMD between the two arms was significant ($P = 0.008$)

improvements in LS-BMD occurred within the first 6 months after treatment. However, there was no significant change in LS-BMD in the placebo arm [Table 3]. There was no significant change from baseline in FN-BMD at 6 months and 12 months in either arm [Tables 2 and 3]. TH-BMD increased in the ZA arm, but no significant change was seen in the placebo arm [Tables 2 and 3]. However, BMD changes at TH in the ZA arm were within the LSC.

Changes in TBS

At the end of the study, there was no significant change in TBS in either arm [Tables 2 and 3]. In addition, there were no between-arm differences in TBS at 6 and 12 months [Table 4].

Changes in BTMs

Both β-CTX and P1NP significantly reduced in the ZA arm [Table 2]. However, there was no significant change in either BTM in the placebo arm [Table 3]. There was a significant difference between the two arms in the change in β-CTX levels at 6 and 12 months. However, there was a significant difference in P1NP levels between the two arms at 6 months but not at 12 months [Table 4].

Vertebral fractures (VF)

Eleven patients in the ZA arm and five in the placebo arm had 25 VFs at baseline (24 grade 1 and one grade 2). There were nine new grade 1 VFs in the ZA arm and 14 new grade 1 VFs in the placebo arm. One patient in the ZA arm had a fracture deterioration from grade 1 to grade 2. Seven patients in the ZA arm and nine in the placebo arm developed new VFs ($P = 0.239$). In addition, two patients in the ZA arm and three in the placebo arm developed 2 VFs ($P = 0.628$). SFI increased significantly in both arms [Tables 2 and 3]. There was no difference in SFI between the two arms at 6 and 12 months [Table 4].

Adverse events

Six of the nineteen patients (31.6%) in the ZA arm had adverse reactions, and none in the placebo arm developed adverse reactions.

Discussion

Current treatment recommendations for HOD are based on the postmenopausal osteoporosis literature.[3] Most studies evaluating the effect of bisphosphonates in pre-transplant HOD have been conducted in patients with primary biliary cirrhosis (PBC).[8-16] Oral bisphosphonates' effect on BMD using alendronate, risedronate and ibandronate has been studied in non-cholestatic liver cirrhosis. They effectively improved BMD in such patients.[17,18] No dose adjustments are required for bisphosphonates in HOD.

Currently, no studies of pre-transplant HOD using ZA, the standard bisphosphonate used in postmenopausal osteoporosis, have been reported.[19] Therefore, we conducted this study to investigate the effect of ZA in pre-transplant HOD.

Effect of ZA on BMD

In our study, the mean percentage increase in LS-BMD was 5.11 (3.50) in the ZA arm and 0.72 (4.63) in the placebo arm at

Table 3: Trend of changes in various parameters in the placebo arm

Parameter		0 m	6 m	12 m	*P* (0-6-12)	*P* (0-12)	*P* (0-6)	*P* (6-12)
LS-BMD	g/cm²*	0.741 (0.067)	0.746 (0.079)	0.748 (0.073)	0.678			
	Z-score*	-2.87 (0.644)	-2.81 (0.789)	-2.8 (0.75)	0.666			
FN-BMD	g/cm²**	0.669 (0.609-0.699)	0.674 (0.590 – 0.734)	0.654 (0.587-0.736)	0.640			
	Z-score**	-1.45 (-1.70 - -0.775)	-1.15 (-1.78 - -0.130)	-1.45 (-1.85- -0.550)	0.975			
TH-BMD	g/cm²*	0.761 (0.097)	0.760 (0.105)	0.756 (0.090)	0.706			
	Z-score**	-1.80 (-1.98 - -1.23)	-1.75 (-2.08 - -1.13)	-1.7 (-2 - -1.2)	0.898			
TBS*		1.30 (0.06)	1.32 (0.06)	1.32 (0.07)	0.355			
β-CTX (ng/ml)*		0.509 (0.146)	0.467 (0.204)	0.544 (0.160)	0.310			
P1NP (ng/ml)*		84.5 (32.8)	79.8 (27.3)	75.3 (26.6)	0.367			
SFI**		0.036 (0.009-0.241)	0.214 (0.045-0.313)	0.268 (0.134-0.375)	<0.001	0.002	0.011	0.005

*mean±SD; **median (IQR). LS-BMD – lumbar spine bone mineral density; FN-BMD – femoral neck bone mineral density; TH-BMD – total hip bone mineral density; TBS – trabecular bone score; β-CTX – beta-C-terminal telopeptide; P1NP – procollagen 1 intact N-terminal propeptide; SFI – spinal fracture index

Table 4: Comparison between the groups at 12 months

Parameter		ZA arm	Placebo arm	*P*
eGFR (ml/min)*		93.9 (19.4)	103 (13.0)	0.183
Calcium (mg/dl)*		9.14 (0.50)	9.02 (0.46)	0.505
Phosphate (mg/dl)*		3.03 (0.67)	3.29 (0.57)	0.289
Intact PTH (pg/ml)*		44.9 (27.0)	40.7 (19.8)	0.654
25(OH)D (ng/ml)**		27.7 (23.6-35.7)	32.2 (22.8-44.1)	0.845
LS-BMD	g/cm²*	0.817 (0.045)	0.749 (0.071)	0.005
	Z-score*	-2.13 (0.381)	-2.78 (0.722)	0.01
FN-BMD	g/cm²*	0.726 (0.117)	0.664 (0.102)	0.154
	Z-score*	-0.800 (0.888)	-1.25 (0.781)	0.173
TH-BMD	g/cm²*	0.829 (0.090)	0.749 (0.090)	0.028
	Z-score*	-1.03 (0.605)	-1.57 (0.610)	0.026
TBS**		1.29 (1.23-1.35)	1.32 (1.28-1.37)	0.240
β-CTX (ng/ml)**		0.254 (0.161-0.373)	0.560 (0.480-0.620)	0.007
P1NP (ng/ml)*		65.9 (28.8)	75.3 (26.6)	0.393
ALP (IU/L)**		85.0 (73.0-129)	108 (90.3-126)	0.430
SFI*		0.195 (0.110)	0.259 (0.132)	0.184

* mean (SD); **median (IQR). LS-BMD – lumbar spine bone mineral density; FN-BMD – femoral neck bone mineral density; TH-BMD – total hip bone mineral density; TBS – trabecular bone score; β-CTX – beta-C-terminal telopeptide; P1NP – procollagen 1 intact N-terminal propeptide; ALP – alkaline phosphatase; SFI – spinal fracture index

12 months. LS-BMD in the ZA arm increased more than LSC, while there was no worsening in the placebo arm. In an RCT conducted on patients with PBC, alendronate and ibandronate improved LS-BMD by 4.6% and 3.8%, respectively, at 12 months.[16] Similarly, in patients with postmenopausal osteoporosis, ZA has improved LS-BMD by 3.6 to 4.4% at the end of 12 months.[20,21] The LS-BMD changes observed in our study were similar to previous bisphosphonate studies.

The mean percentage increase in FN-BMD was 1.59 (4.11) in the ZA arm at 12 months, while there was a mean percentage decrease in FN-BMD of 1.02 (5.35) in the placebo arm. In an RCT conducted in patients with PBC, alendronate and ibandronate improved FN-BMD by 1.43% and 1.01%, respectively, at 12 months.[16] Reid *et al*.[20] found a placebo-adjusted improvement in FN-BMD of 3.1 to 3.5% with different ZA doses. Similarly, there was a mean percentage increase in TH-BMD of 1.49 (3.23) in the ZA arm and a mean percentage decrease of 0.83 (2.81) in the placebo arm at 12 months. Alendronate improved TH-BMD by 1.74%, while ibandronate improved it by 1.42% at 12 months in an RCT conducted in patients with PBC.[16] In a study conducted on Chinese women with osteoporosis, ZA showed a placebo-adjusted 2.12% increase in TH-BMD at the end of 1 year.[22] Although the changes in FN-BMD and TH-BMD in our study were similar to previous studies, the changes cannot be considered clinically significant as they were within the LSC in both arms.

In our study, the increase in LS-BMD in the ZA arm was similar to that documented in previous studies. However, the improvements in FN-BMD and TH-BMD were within the LSC. ZA improves trabecular bone density more effectively than cortical bone density.[23] The spine is predominantly composed of trabecular bone (66%) compared to FN (25%) and TH (50%).[24] This different composition of skeletal sites may explain the variation of the ZA effect at different sites. However, long-term follow-up over 3 years has shown that ZA increases FN-BMD and TH-BMD by 5.06% and 6.02%, respectively.[25]

Effect of ZA on TBS

Mean TBS at baseline ranged from 1.20 to 1.35, indicating partially degraded bone in both arms. The mean percentage increase in TBS was 0.56 and 1.58 in the ZA and placebo arms, respectively, both of which were below the conservative estimate of the LSC for TBS (5.8%).[26] In our study, despite a significant increase in LS-BMD, there was no significant improvement in TBS in the ZA arm. In a study examining the effect of ZA on bone microarchitecture in male participants with non-metastatic prostate cancer undergoing androgen deprivation therapy, there was no significant improvement in bone microarchitecture in the ZA arm despite an increase in BMD.[27] This phenomenon can be explained by the failure of ZA to completely suppress imbalanced bone remodelling, together with its inability to penetrate and distribute in sufficient quantity into deeper cortical bone tissue.[27]

Effect of ZA on BTMs

β-CTX levels showed a decreasing trend in the ZA arm (median percentage decrease of 43.22 at 12 months), while in the placebo arm, they initially decreased at 6 months (median percentage decrease of 10.3) but showed an increasing trend at 12 months (median percentage increase of 10.47). Changes in β-CTX levels were statistically different between the two arms at 6 and 12 months ($P = 0.001$). Alendronate and ibandronate reduced β-CTX levels by 60.5% and 59.52%, respectively, over 12 months in patients with PBC.[16]

P1NP levels showed a decreasing trend in the ZA arm. Changes in P1NP levels were statistically different between the two arms at 6 months ($P = 0.017$) but not at 12 months ($P = 0.17$). In a study conducted in patients with PBC, alendronate and ibandronate reduced P1NP levels by 48.12% and 46.35%, respectively, over 12 months.[16]

In our study, BTMs decreased significantly in the ZA arm. The changes in BTM in our study were similar to those in the previous studies but of a smaller magnitude. This may be due to increased P1NP and β-CTX levels in patients with liver disease due to an increase in hepatic type 1 collagen.[28]

Effect of ZA on VFs and SFI

There was a significant worsening of the SFI in both arms. This deterioration was observed at time intervals of 0–6 months and 6–12 months in both arms. ZA was similar to placebo in terms of SFI at all time points. In addition, the number of patients developing new VFs and those developing 2 VFs was similar in both arms. ZA has been shown to prevent VFs in postmenopausal osteoporosis.[20,21] Similarly, previous studies performed in PBC using alendronate and ibandronate have shown that they effectively prevent VFs.[13,14,16] However, these studies were performed on women with PBC with a higher body mass index (BMI) than our patients. The risk factors for fragility fractures in HOD are low BMD, deterioration of trabecular microarchitecture, malnutrition, toxic effects of alcohol and an increased tendency to fall.[1,3] Therefore, although ZA effectively improved LS-BMD, it may not prevent fragility fractures in HOD. This may likely be due to the presence of other factors that increase the risk of fragility fractures.

In our study, six (31.6%) patients in the ZA arm experienced acute phase reactions. Three (15.8%) patients developed fever, while the remaining three (15.8%) developed fever and myalgia. Side effects appeared within three days of drug administration. The incidence of side effects in our study was comparable to that observed in other studies. None of our patients developed serious side effects such as atrial fibrillation, symptomatic hypocalcaemia or ocular inflammation.

The key strength of our study is its double-blind, RCT design. Our study is the first to analyse the effects of ZA in patients with pre-transplant HOD. In addition, we quantitatively analysed the incidence of VFs using the SFI. Although our study had the limitation of not reaching the calculated sample size, the *post hoc* power for the primary outcome was adequate. The other limitations of our study were the short duration of follow-up (1 year may not be sufficient to comment on long-term trends in BMD and VF) and the use of collagen-based BTMs such as P1NP and β-CTX (non-collagen-based BTMs would have been a better alternative).

Conclusion

ZA was effective in improving LS-BMD in male patients with HOD. Although there was no change in TBS and VF rates with ZA, the study was not sufficiently powered to assess these outcomes. Similar studies of longer duration that are adequately powered to assess TBS and VFs are needed to better understand the role of ZA in pre-transplant HOD.

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Conflicts of interest

There are no conflicts of interest.

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