Journal of Bone and Mineral Metabolism (2019) 37:996–1003
https://doi.org/10.1007/s00774-019-01003-1

ORIGINAL ARTICLE

# Comparative effectiveness of alendronate and zoledronic acid on bone mass improvement in transfusion-dependent thalassemia patients

**Omid Reza Zekavat[1] · Mohamadreza Bordbar[1] · Sezaneh Haghpanah[1] · Forough Saki[2] · Asghar Bazrafshan[1] · Haleh Bozorgi[1]**

Received: 28 October 2018 / Accepted: 29 March 2019 / Published online: 11 April 2019


## Abstract

Thalassemia, as the most prevalent genetic blood disorder, has many associated comorbidities including low bone mass. We studied the comparative effectiveness of alendronate (AL) and zoledronic acid (ZOL) on bone mass improvement in transfusion-dependent thalassemia (TDT) patients a year after treatment. Three hundred seventy-five TDT patients with low bone mass were enrolled in this study. After a year of treatment with either AL or ZOL, a second bone mineral density (BMD) test was ordered to compare the effectiveness of the two aforementioned drugs. Body mass index (BMI), physical activity, sun exposure, and biochemical laboratory data were also considered as associated factors in this study. The BMD test of both groups was almost the same at the baseline and it increased comparably after a year of treatment with AL and ZOL. However, there was a significant difference in lumbar spine BMD delta *Z* score between both groups of female patients. ZOL was more effective in increasing the lumbar spine BMD of female patients. The choice of bisphosphonates therapy (oral versus parenteral) should be individually selected by considering patient's preference, compliance and the physician's decision. Given the longer administration interval, and TDT patients' compliance issue, it is justified to recommend ZOL as the drug of choice for patients suffering from low bone mass.

**Keywords** Bone density · Beta-thalassemia · Alendronate · Zoledronic acid

## Introduction

According to the World Health Organization (WHO), thalassemia is the most prevalent genetic blood disorder. As said by the censuses, there are approximately 26,000 thalassemia patients in Iran [1]. Transfusion-dependent thalassemia (TDT) patients face long-term complications, which requires ongoing treatment and follow-up. TDT patients' longevity has increased noticeably over the years, using regular blood transfusions and iron chelating therapy [2]. Today, with more TDT patients reaching their third and fourth decades of life, age-related complications are more evident, which is a serious source of morbidity, such as bone mineral density disorder [3].

Initially, this disorder presents itself with facial and cranial bones deformity due to bone marrow expansion caused by ineffective erythropoiesis, which is typical in TDT patients [4]. Later, various risk factors including iron overload, vitamin D deficiency, hypocalcemia, hypogonadism, growth hormone deficiency, insulin growth factor deficiency, and Desferrioxamine toxicity might gradually lead to early onset of low bone mass [5, 6].

Normal bone mass is indicative of a balance between osteoblasts bone formation and osteoclasts bone resorption. Dual-energy X-ray absorptiometry (DXA) of the lumbar spine and femoral neck is a practical method, available for measuring BMD [7]. The criteria we used to confirm low bone mass in TDT patients were according to the definition of the International Society for Clinical Densitometry (ISCD) [8].

Low bone mass in TDT patients requires a treatment which does not only slow down the process, but it is also preventative. Bisphosphonates (BP)s can increase BMD by inhibiting osteoclasts' bone resorption. The basic mechanism is to prevent osteoclasts maturation and induce apoptosis [9].

✉ Haleh Bozorgi
bozorgihaleh@yahoo.com

[1] Hematology Research Centre, Nemazee Hospital, Shiraz University of Medical Sciences, 7193635899 Shiraz, Iran

[2] Endocrinology and Metabolism Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Hence, BPs seem to represent an ideal class of drugs for treating low bone mass. Alendronate (AL) is an approved oral BP which has been shown to be effective in increasing bone density [10]. Another BP, zoledronic acid (ZOL), was recently evaluated in TDT patients and determined to successfully improve BMD [11, 12]. Therefore, this study aimed to compare the efficacy of both ZOL and AL in TDT patients in treating low bone mass while considering other associated factors, such as physical activity, sun exposure, body mass index (BMI), serum vitamin D, calcium (Ca), and phosphorus (Ph) levels.

## Materials and Methods

### Population

The subjects of this historical cohort study were selected from 734 TDT patients who had registered from March 2016 to September 2017 in the comprehensive thalassemia center in Dastgheib hospital, affiliated to Shiraz University of Medical Sciences, Iran. All patients older than 9 years with confirmed LBM (a *Z* score of − 2.0 or lower than the expected range for age based on ISCD's standard) in the femoral neck or lumbar (L1-L4) spines who had been newly treated with either AL or ZOL for at least a year were included. Those with impaired renal and liver function, previous bisphosphonates treatments, and other forms of thalassemia including sickle-thalassemia and HbE-β thalassemia were excluded from the study, resulting in 359 exclusions. Patients were not on anticonvulsants drugs of any kind or corticosteroids for the past 12 months prior to the BMD. Also, there were no record of malabsorption syndromes (e.g., Crohn's colitis, ulcerative colitis, cystic fibrosis, history of bariatric surgery) amongst our patients. The prevalence of other endocrine disorders in the remaining 375 TDT patients were hypogonadism (64.5%), diabetes mellitus (DM) (23.5%), hypoparathyroidism (18.4%) and hypothyroidism (7.7%).

Proper treatment of each endocrinopathy was determined for the patients during their annual endocrinologist visit: Levothyroxine for those with hypothyroidism, Calcitriol 0.25–2.0 μg/day and calcium 1 g of calcium/day for those with hypoparathyroidism, either oral anti-diabetic agents or insulin therapy was prescribed for DM patients as appropriate and hormonal replacement therapy was utilized for hypogonadic patients. An informed written consent form was obtained from the participants. The study was approved by the local Ethics Committee of Shiraz University of Medical Sciences with the code number of 5359.

### Treatment and BMD test assessment

Patients with confirmed LBM were divided into two groups of treatment. One group was treated with AL (Fosamax, Merck & Co., Inc) 70 mg weekly for a total duration of 1 year. The second group were treated with ZOL (Zometa, Novartis®) 4 mg (0.05 mg/kg in children) Iv infusion over 30 min twice a year (6 months apart). They were all eligible for receiving dosage of 4 mg. All patients were prescribed to take supplements of calcium 500 mg and vitamin D 400 IU daily. Patients with vitamin D deficiency received weekly 50,000-unit vitamin D pearl for 8 weeks before starting bisphosphonates. In addition, patients with hypogonadism and other endocrinopathies were under direct supervision of endocrinologist and were receiving the required treatment.

The second BMD test was performed (as a part of the routine annual checkup) 12 months after initiating the treatment and the results were compared with the pre-treatment BMD. The lumbar spines (L2–L4) and right femoral neck BMD were measured using Hologic system DXA (Discovery QDR, USA). The data of Hologic system DXA from the US Center for Disease Control's "National Health and Nutrition Examination Survey" (NHANES) was used to interpret the bone density *Z* scores and normative data.

### Safety and fracture

The patients were informed about the possible side effects of both drugs, such as gastrointestinal toxicity for AL, and fever/musculoskeletal pain for ZOL. The patients were asked to provide a report during monthly visits, if they had experienced any drug-related symptoms. Hematology and biochemistry labs were tested before and after receiving both drugs. All unpleasant and unintentional clinical features were considered as adverse effects, and were appraised in terms of onset, duration and outcome by our physicians. There were no reported fractures amongst participants in the course of study.

### Contributing factors

Sun exposure, physical activity, serum 25(OH) vitamin D, Ca and Ph levels, and BMI were also evaluated. Patients filled out a form that classified physical activity into three groups suggested by the American College of Sports Medicine: no physical activity, 1 h of physical activity less than three times a week, and at least 1 h of physical activity more than three times a week. To evaluate the

amount of sun exposure experienced by each patient, they were self-classified into three categories: less than 15 min, 15–30 min, and more than 30 min a day of direct sun exposure [1].

A technician took 5 ml venous blood after 8–12 h of fasting during the yearly routine workup. Serum Ca and Ph were checked using colorimetric method with an auto-analyzer (Biosystem SA, Barcelona, Spain). 25-OH vitamin D levels were evaluated using electrochemiluminescent methods with Cobas 411 (Roche, Germany). Patients were classified into three groups with respect to their serum 25(OH) vitamin D level: sufficient (> 50 nmol/L), insufficient (30–50 nmol/L), and deficient (< 30 nmol/L) according to Institute Of Medicine (IOM) [13]. Daily vitamin D tablet 400 IU was prescribed for the latter two groups. BMI was measured and calculated by a trained health professional. Height was measured by a standard wall mounted meter and rounded to the nearest 0.5 cm. Weight was assessed via a standard scale (Seca, Germany), while the patients were wearing a light dress with shoes off. BMI was calculated using the standard formula, BMI ($kg/m^2$) = weight(kg)/[height($m^2$)], and classified into four group: underweight (< 18.5), healthy (18.5–24.9), overweight (25.0–29.9), and obese (> 30) [14].

### Statistical analysis

Data analysis was performed using SPSS, version 21. Descriptive data was presented in terms of mean, standard deviation, and 95% confidence interval. In each group bone mass indices were compared by Paired *t* test before and after treatment. Comparison of qualitative and quantitative variables between the two groups was done by $\chi^2$ test and Student's *t* test respectively. *P* values less than 0.05 were considered to be statistically significant.

## Results

The mean age of the 375 TDT patients in the study was 29.1 ± 8 years [AL-treated group: 28.6 ± 8.8 (14–62), Zol-treated group: 29.8 ± 6.7 (15–51)] and 58.1% of them were female. Table 1 shows the general characteristics and laboratory data of both groups (treated with AL or ZOL). Although age was matched in both groups, gender distribution was significantly different between the two ($P = 0.008$). Patients in both groups had similar bone mass indices before starting the treatment ($P < 0.05$). Considering the potential contributing factors such as BMI, Ca, Ph, sun exposure, and physical activity, there was no significant difference between the two groups. Despite taking vitamin D supplements, more than half of the patients in both groups had vitamin D deficiency.

DXA characteristics of both groups as well as the mean differences are summarized in Table 2. Lumbar spines BMD was significantly improved in both treatment groups, and the treatment effect was comparable in both groups. Conversely, Lumbar spines *Z* score were improved only in the ZOL-treated arm. With regards to femoral neck BMD, neither ZOL nor AL could improve bone loss. On the other hand, femur neck *Z* score was increased in both groups without difference in treatment effect between the two drugs (Table 2).

Since gender distribution was significantly different between the AL and ZOL-treated groups, the analysis was repeated amongst females and males separately. The results revealed that the significant difference was more related to the female group ($P = 0.01$). ZOL increased lumbar *Z* score compared to AL only in the female strata (Table 3). Other variables such as age, height, weight, and BMI had no impact on the efficacy of the drugs. None of the bisphosphonates adverse event led to discontinuation of treatment (Table 4).

Since prevalence of hypoparathyroidism, an endocrine disorder with direct impact on bone mass, was 18.4% amongst our patients (variable mean duration time: 9 months–7 years), we excluded those with hypoparathyroidism and redid the analysis and achieved the same results. However, the treatment effect of ZOL on lumbar *Z* score in female subject was reduced, though it remained marginally significant ($P = 0.051$ 95% CI − 0.34 to 0.0007).

## Discussion

This study revealed that both AL and ZOL improved bone mass after a year of treatment in both femoral neck and lumbar spine of TDT patients; however, ZOL was more effective in female patients particularly in the lumbar spines area. Treatment of underlying endocrine disorders, particularly hypoparathyroidism and hypogonadism might help to achieve better results. Age, physical activity, sun exposure, BMI, as well as serum vitamin D, Ca, and Ph did not affect the efficacy of either ZOL or AL.

Low bone mass is a major cause of morbidity in TDT patients, caused by a variety of risk factors, different from risk factors for non-transfusion-dependent thalassemia patients. The impaired bone turnover is due to augmentation of bone reabsorption by osteoclasts, and reduction of osteoblasts caused by iron overload. In addition, bone marrow expansion due to ineffective erythropoiesis results in thinning of the cortex, making bones more prone to fractures [15–17].

Studies have suggested a correlation between the amount of bone mass and serum level of Ca, Ph, 25-(OH) vitamin D, ferritin as well as each individual's gender, age, BMI, physical activity, and amount of sun exposure. Additionally, hypoparathyroidism acknowledged effects on bone mass was our consideration and verified its effect on bone mass by

**Table 1** Pre-treatment general characteristics and laboratory data of the study population

| Variable | Alendronate- treated, *n* (218) | Zoledronate acid- treated, *n* (157) | *P* value |
|---|---|---|---|
| Weight (kg) (mean ± SD) | 51.6 ± 10.1 | 52 ± 8.2 | 0.646 |
| Height (cm) (mean ± SD) | 159 ± 10 | 158 ± 9.7 | 0.458 |
| BMI (%) | | | 0.171 |
| < 18.5 | 26.2 | 18.5 | |
| 18.5–24.9 | 68.7 | 78.3 | |
| 25–29.9 | 3.7 | 3.2 | |
| 30 ≤ | 1.4 | 0 | |
| Age (year) (mean ± SD) | 28.6 ± 8.8 | 29.8 ± 6.7 | 0.127 |
| Gender (%) | 52.3 | 66.2 | 0.008* |
| Female | 47.7 | 33.8 | |
| Male | | | |
| Calcium (mg/dl) (mean ± SD) | 9.4 ± 0.7 | 9.5 ± 2.4 | 0.957 |
| Phosphorous (mg/dl) (mean ± SD) | 4.4 ± 1.2 | 3.8 ± 1.3 | 0.054 |
| 25 (OH) $D_3$ (%) | | | 0.978 |
| < 30 nmol/L | 63 | 64 | |
| 30–50 nmol/L | 22 | 22 | |
| > 50 nmol/L | 15 | 14 | |
| Sun exposure (%) | | | |
| Group 1 | 28 | 36 | 0.279 |
| Group 2 | 45 | 41 | |
| Group 3 | 27 | 23 | |
| Physical activity (%) | | | 0.389 |
| Group 1 | 13.3 | 14.1 | |
| Group 2 | 50.9 | 43.9 | |
| Group 3 | 35.8 | 42 | |
| Parathyroid hormone (ng/L) (mean ± SD) | 31.76 ± 27.84 | 37.83 ± 29.32 | 0.533 |
| Diabetes mellitus (%) | 21.6 | 26.1 | 0.325 |
| Hypogonadism (%) | 62.4 | 67.5 | 0.326 |
| Hypothyroidism (%) | 7.8 | 7.6 | 1 |
| Hypoparathyroidism (%) | 16.1 | 21.7 | 0.179 |

Vitamin D classification: (1) (< 30 ng/ml): deficient, (2) (30–50 ng/ml) insufficient, (3) (> 50 ng/ml) sufficient

Sun exposure classification: (1) less than 15 min, (2) 15–30 min and (3) more than 30 min a day of direct sun exposure

Physical activity classification: (1) no physical activity, (2) 1 h of physical activity less than three times a week and (3): 1 h of physical activity more than three times a week

*BMI* sbody mass index, *DXA* dual-energy X-ray absorptiometry

*Statistically significant

some differences in results after excluding patients with this disorder [18].While different treatment options have been used to improve low bone mass in TDT patients, BPs remain to be the treatment of choice [9]. Since prior research have identified AL and ZOL as more efficient BPs, our study aimed to compare the effectiveness of these two drugs.

Our results showed that both drugs had a similar effect on bone mass improvement. However, when we compared the mean *Z* score difference of the lumbar spines bone mass, ZOL was shown to be more effective in female patients. With respect to male patients, the drugs showed equal efficacy in improving low bone mass, which was in agreement with the study by Orwoll et al. [19]. When we excluded patients with hypoparathyroidism and repeated the analysis, ZOL preference over AL in female patients became less significant. The fact that bone loss is different between genders amongst patients with thalassemia [16], the borderline result ($P = 0.051$) after gender stratification calls for further studies. Male participants with thalassemia suffer from bone loss more than their

**Table 2** Comparison of the DXA characteristic indices between the two studied groups

| Variable | Alendronate-treated n (218) | Zoledronic acid-treated n (157) | *P* value 1 | Mean difference 1 (95% CI) |
|---|---|---|---|---|
| Pre-treatment lumbar spine L2–L4 BMD ($g/cm^2$) | 0.69 ± 0.1 | 0.69 ± 0.09 | 0.343 | − 0.01 (− 0.03 to 0.01) |
| Post-treatment lumbar spine L2–L4 BMD ($g/cm^2$) | 0.71 ± 0.09 | 0.71 ± 0.08 | 0.504 | − 0.007 (− 0.02 to − 0.01) |
| Mean difference 2 lumbar spine L2–L4 BMD ($g/cm^2$) (95% CI) | 0.01 (0.004–0.02) | 0.02 (0.01–0.03) | 0.490 | 0.005 (− 0.02 to 0.01) |
| *P value 2* | 0.007* | < 0.001* | – | – |
| Pre-treatment lumbar spine L2–L4 *Z* score | − 3.06 ± 0.99 | − 3.2 ± 0.76 | 0.445 | 0.07 (− 0.11 to 0.25) |
| Post-treatment lumbar spine L2–L4 *Z* score | − 3.04 ± 0.83 | − 3.01 ± 0.81 | 0.728 | − 0.03 (− 0.23 to 0.16) |
| Mean difference 2 lumbar spine L2–L4 *Z* score (95% CI) | 0.01 (− 0.10 to 0.12) | 0.21 (0.10–0.32) | 0.013* | 0.20 (− 0.36 to − 0.04) |
| P value 2 | *0.844* | < 0.001* | – | – |
| Pre-treatment femoral neck BMD ($g/cm^2$) | 0.60 ± 0.11 | 0.59 ± 0.10 | 0.317 | 0.01 (− 0.01 to 0.03) |
| Post-treatment femoral neck BMD ($g/cm^2$) | 0.60 ± 0.10 | 0.60 ± 0.09 | 0.981 | − 0.0003 (− 0.02 to 0.02) |
| Mean difference 2 femoral neck BMD ($g/cm^2$) (95% CI) | − 0.006 (− 0.01 to 0.004) | 0.003 (− 0.01 to 0.01) | 0.264 | 0.01 (− 0.02 to 0.007) |
| P value 2 | *0.237* | *0.640* | – | – |
| Pre-treatment femoral neck *Z* score | − 2.3 ± 0.9 | − 2.3 ± 0.9 | 0.978 | 0.002 (− 0.19 to 0.19) |
| Post-treatment femoral neck *Z* score | − 2.2 ± 0.79 | − 2.1 ± 0.94 | 0.230 | − 0.12 (− 0.33 to 0.08) |
| Mean difference 2 femoral neck *Z* score (95% CI) | 0.11 (0.02 - 0.20) | 0.26 (0.10–0.42) | 0.110 | 0.14 (-.032 - 0.02) |
| *P* value 2 | 0.011* | 0.001* | – | – |

Mean difference show the difference between the densitometry indices before and after treatment

*BMD* bone mineral density, *DXA* dual-energy X-ray absorptiometry

*P* value and Mean difference 1 are regarding to comparison of DXA characteristics between both treated groups

*P* value and Mean difference 2 are regarding to comparison of DXA characteristics of each drug before and after treatment

*Statistically significant

**Table 3** Comparison of the mean differences values of the first and second bone mineral density indices in the treatment groups in both genders

| DXA characteristics | Alendronate-treated women | Zoledronic acid-treated women | *P* value | Alendronate-treated men | Zoledronic acid-treated men | *P* value |
|---|---|---|---|---|---|---|
| Mean difference lumbar spine L2-L4 BMD ($g/cm^2$) | 0.01 (− 0.004 to 0.02) | 0.01 (0.006 to 0.03) | 0.589 | 0.02 (0.004 to 0.04) | 0.03 (0.007 to 0.06) | 0.430 |
| Mean difference lumbar spine L2-L4 *Z* score | − 0.007 (− 0.10 to 0.12) | 0.19 (0.07 to 0.28) | 0.017* | 0.02 (− 0.21 to 0.23) | 0.28 (− 0.01 to 0.57) | 0.163 |
| Mean difference femoral neck BMD ($g/cm^2$) | − 0.01 (− 0.02 to 0.003) | − 0.00 (− 0.01 to 0.01) | 0.396 | − 0.002 (− 0.01 to 0.02) | 0.01 (− 0.01 to 0.04) | 0.326 |
| Mean difference femoral neck *Z* score | 0.06 (− 0.06 to 0.14) | 0.26 (0.05 to 0.39) | 0.062 | 0.18 (0.03 to 0.34) | 0.27 (0.05 to 0.58) | 0.605 |

*Statistically significant

female counterparts. This difference also varies in different regions of the body. Pollak et al. showed that men with thalassemia experience bone mass changes mostly in spinal region in contrast to female. Having not considered bone mass changes, comparing basic DXA characteristics of patients with thalassemia revealed that women face low

**Table 4** Adverse effects of both Alendronate and Zoledronic acid through 1-year study

| Adverse effects | Alendronate-treated | Adverse effects | Zoledronic acid-treated |
|---|---|---|---|
| Abdominal pain (%) | 6.2 | Influenza-like symptoms (%) | 36.5 |
| Esophagitis (%) | 0.8 | Myalgia (%) | 14 |
| Acid regurgitation (%) | 13.4 | Arthralgia (%) | 1.3 |
| Dyspepsia (%) | 2.2 | Skin disorders (%) | 0 |
| Heartburn (%) | 10 | Headache (%) | 21.3 |
| Nausea (%) | 16.8 | Fever (%) | 52.4 |

bone mass mostly in lumbar spine while men mostly experience it in femoral neck. It is anticipated to observe more bone loss in spinal region due to its trabecular structure in comparison with cortical structure of femoral neck, but previous studies showed inconsistent results [20, 21]. We also concluded that bisphosphonates and ZOL in particular are more effective in improving bone mass in the lumbar spines, and not in femoral neck.

Although it is postulated that a single dose of ZOL infusion might reduce bone resorption markers more quickly than weekly oral AL, we could not show such a difference in terms of efficacy with regards to other associated factors that were previously noted [22]. Shirani et al. evaluated the effect of AL in TDT patients with low bone mass reporting a significant improvement in bone mass density without any severe side effects [23]. Various studies compared AL with other available BPs to determine the most efficacious treatment in TDT patients. Morabito et al. compared the effect of AL and Clodronate versus the placebo group and showed AL to be more efficient in improving bone mass [24].

A comprehensive study on the effect of BPs was conducted by Giusti comparing AL, ZOL and Neridronate with paired placebo groups. Although all three drugs significantly improved bone mass in TDT patients, they were not compared with each other to determine the most efficacious one [4].

In a recent study on non-thalassemic population by Boonen et al. ZOL improved bone mass equally in both genders [25]. McClung et al. proved the efficacy of ZOL in reducing bone loss in postmenopausal women with LBM by comparing the ZOL-treated group with placebo [26]. Gilfillan et al. also confirmed the effectiveness of ZOL by comparing BMDs of TDT patients treated with ZOL and a placebo group [7]. While studying the effect of ZOL on bone mass, positive results in reducing bone pain in TDT patients were observed by Voskaridou et al. focused on the proper dosage and interval of ZOL, indicating that this drug seems to be dose dependent with more efficacy at shorter intervals. Even though ZOL continues to improve bone mass for at least 3 years after its discontinuation, there are few experiences on how long the drug can be safely continued [15, 27–29].

Despite improvements in bone mass by AL and ZOL, drug side effects as well as patient compliance must be considered while choosing which drug to use and what dosages to prescribe for patients. One of the serious side effects of all BPs is atypical femoral shaft fracture. Gastrointestinal upset is the main side effect of AL, which necessitates the reformulation of the drug with less gastrointestinal irritant ingredients [28, 30]. One last thing to consider is the potency of prescribed drugs. ZOL is the most potent bisphosphonates ever used in patients with thalassemia major, hence, comparing other bisphosphonate like AL with ZOL requires longer duration and follow-up to reach more reliable results [16]. Since TDT patients suffer from multiple complications, and they have to consume many drugs, they usually prefer to use medications with less frequent intervals. In our experience, TDT patients were more satisfied with using ZOL infusion every 6 months than taking AL orally every week which has a pivotal role in their compliance leading to higher efficacy.

Our study is the first study in Middle East which tried to compare two generations of BPs (AL and ZOL) in TDT patients. It is noteworthy to mention that the evaluation was done in Iran, one of the countries located in the thalassemia belt and in a comprehensive thalassemia center. Moreover, many associated risk factors of low bone mass were also considered.

Despite the above-mentioned strengths, this study faced some limitations. First, it was a retrospective study and the data were gathered through reviewing the electronic health records of our patients. Therefore, we did not have any role in randomizing the patients to any consumed drug or omitting any possible confounding factor. Additionally, while we had more than 500 patients identified to have low bone mass in our initial screening, more than 100 patients had to be excluded as they did not have the second DXA scan. This also reinforces the necessity of a multi-center randomized clinical trial to assess and compare the long-term safety and efficacy of these two drugs and possibly new generations of BPs in TDT patients.

In conclusion, both ZOL and AL improved bone mass in TDT patients, but ZOL was more effective particularly in females. There was no significant difference in terms of other possible contributing factors of LBM between

ZOL-treated and AL-treated patients. Given the longer interval of administration and the compliance issue of TDT patients, it is advisable to recommend ZOL as the drug of choice in TDT patients suffering from LBM. A larger prospective multi-center clinical trial is warranted to assess the long-term safety and efficacy of both drugs while considering the quality of life as a major determinant.

**Acknowledgement** This study was produced as a part of Haleh Bozorgi doctoral thesis with the specified grant number of 15195 provided by Shiraz University of Medical Science. We thank Shirin Parand at the Hematology Research Center for preparation of the manuscript. The authors wish to thank Sara Dadashzadeh and Mr. H. Argasi at the Research Consultation Center (RCC) of Shiraz University of Medical Sciences for his invaluable assistance in editing this manuscript.

## Compliance with ethical standards

**Conflict of interest** Omid Reza Zekavat, Mohamadreza Bordbar, Sezaneh Haghpanah, Forough Saki, Asghar Bazrafshan and Haleh Bozorgi declare that they have no conflict of interest.

## References

1. Maheri A, Sadeghi R, Shojaeizadeh D, Tol A, Yaseri M, Ebrahimi M (2016) Associations between a healthpromoting lifestyle and quality of life among adults with beta-thalassemia major. Epidemiol Health 38
2. Dhirar N, Khandekar J, Bachani D, Mahto D (2016) Thalassemia major: how do we improve quality of life? SpringerPlus 5:1895
3. Hassan MAM, Tolba OA (2016) Iron chelation monotherapy in transfusion-dependent beta-thalassemia major patients: a comparative study of deferasirox and deferoxamine. Electron Phys 8:2425
4. Giusti A (2014) Bisphosphonates in the management of thalassemia-associated osteoporosis: a systematic review of randomised controlled trials. J Bone Miner Metab 32:606–615
5. Morabito N, Gaudio A, Lasco A, Atteritano M, Pizzoleo MA, Cincotta M, La Rosa M, Guarino R, Meo A, Frisina N (2004) Osteoprotegerin and RANKL in the pathogenesis of thalassemia-induced osteoporosis: new pieces of the puzzle. J Bone Miner Res 19:722–727
6. Gaudio A, Morabito N, Xourafa A, Macri I, Meo A, Morgante S, Trifiletti A, Lasco A, Frisina N (2008) Bisphosphonates in the treatment of thalassemia-associated osteoporosis. J Endocrinol Investig 31:181–184
7. Gilfillan C, Strauss B, Rodda C, Bowden D, Kean A-M, Obaid M, Crawford B (2006) A randomized, double-blind, placebo-controlled trial of intravenous zoledronic acid in the treatment of thalassemia-associated osteopenia. Calcif Tissue Int 79:138–144. https://doi.org/10.1007/s00774-019-01003-1
8. Voskaridou E, Terpos E, Spina G, Palermos J, Rahemtulla A, Loutradi A, Loukopoulos D (2003) Pamidronate is an effective treatment for osteoporosis in patients with beta-thalassaemia. Br J Haematol 123:730–737
9. Tsartsalis AN, Lambrou GI, Tsartsalis D, Savvidis C, Karantza M, Terpos E, Kanaka-Gantenbein C, Chrousos GP, Kattamis A (2018) The role of biphosphonates in the management of thalassemia-induced osteoporosis: a systematic review and metaanalysis. Hormones 1–14
10. Voskaridou E, Terpos E (2004) New insights into the pathophysiology and management of osteoporosis in patients with beta thalassaemia. Br J Haematol 127:127–139
11. Sarrai M, Duroseau H, D'Augustine J, Moktan S, Bellevue R (2007) Bone mass density in adults with sickle cell disease. Br J Haematol 136:666–672
12. Ravn P, Weiss SR, Rodriguez-Portales JA, McClung MR, Wasnich RD, Gilchrist NL, Sambrook P, Fogelman I, Krupa D, Yates AJ (2000) Alendronate in early postmenopausal women: effects on bone mass during long-term treatment and after withdrawal. J Clin Endocrinol Metab 85:1492–1497
13. Rosen CJ, Gallagher JC (2011) The 2011 IOM report on vitamin D and calcium requirements for north america: clinical implications for providers treating patients with low bone mineral density (in eng). J Clin Densitom 14:79–84. https://doi.org/10.1016/j.jocd.2011.03.004
14. Lim JU, Lee JH, Kim JS, Hwang YI, Kim TH, Lim SY, Yoo KH, Jung KS, Kim YK, Rhee CK (2017) Comparison of World Health Organization and Asia-Pacific body mass index classifications in COPD patients. Int J Chron Obstruct Pulmon Dis 12:2465–2475. https://doi.org/10.2147/copd.s141295
15. De Sanctis V, Soliman AT, Elsefdy H, Soliman N, Bedair E, Fiscina B, Kattamis C (2017) Bone disease in β thalassemia patients: past, present and future perspectives. Metabolism
16. Terpos E, Voskaridou E (2010) Treatment options for thalassemia patients with osteoporosis. Ann N Y Acad Sci 1202:237–243
17. Jensen C, Tuck S, Agnew J, Koneru S, Morris R, Yardumian A, Prescott E, Hoffbrand A, Wonke B (1998) High prevalence of low bone mass in thalassaemia major. Br J Haematol 103:911–915
18. Duan Y, De Luca V, Seeman E (1999) Parathyroid hormone deficiency and excess: similar effects on trabecular bone but differing effects on cortical bone. J Clin Endocrinol Metab 84:718–722
19. Orwoll ES, Miller PD, Adachi JD, Brown J, Adler RA, Kendler D, Bucci-Rechtweg C, Readie A, Mesenbrink P, Weinstein RS (2010) Efficacy and safety of a once-yearly iv infusion of zoledronic acid 5 mg versus a once–weekly 70-mg oral alendronate in the treatment of male osteoporosis: a randomized, multicenter, double-blind, active-controlled study. J Bone Miner Res 25:2239–2250
20. Perrotta S, Cappellini MD, Bertoldo F, Servedio V, Iolascon G, D'agruma L, Gasparini P, Siciliani MC, Iolascon A, (2000) Osteoporosis in β- thalassaemia major patients: analysis of the genetic background. Br J Haematol 111:461–466. https://doi.org/10.1007/s00774-019-01003-1
21. Pollak RD, Rachmilewitz E, Blumenfeld A, Idelson M, Goldfarb AW (2000) Bone mineral metabolism in adults with β-thalassaemia major and intermedia. Br J Haematol 111:902–907
22. Saag K, Lindsay R, Kriegman A, Beamer E, Zhou W (2007) A single zoledronic acid infusion reduces bone resorption markers more rapidly than weekly oral alendronate in postmenopausal women with low bone mineral density. Bone 40:1238–1243
23. Shirani F, Shahriari-Ahmadi A, Arabi M, Asefi N (2015) Evaluation of alendronate efficacy on bone mineral density in thalassemic patients. Int J Hematol-Oncol Stem Cell Res 6:20–24
24. Morabito N, Lasco A, Gaudio A, Crisafulli A, Di Pietro C, Meo A, Frisina N (2002) Bisphosphonates in the treatment of thalassemia-induced osteoporosis. Osteoporos Int 13:644–649
25. Boonen S, Orwoll E, Magaziner J, Colón-Emeric CS, Adachi JD, Bucci-Rechtweg C, Haentjens P, Kaufman JM, Rizzoli R, Vanderschueren D (2011) Once-yearly zoledronic acid in older men compared with women with recent hip fracture. J Am Geriatr Soc 59:2084–2090
26. McClung M, Miller P, Recknor C, Mesenbrink P, Bucci-Rechtweg C, Benhamou CL (2009) Zoledronic acid for the prevention of bone loss in postmenopausal women with low bone mass: a randomized controlled trial. Obstet Gynecol 114:999–1007. https://doi.org/10.1097/AOG.0b013e3181bdce0a

27. Perifanis V, Vyzantiadis T, Tziomalos K, Vakalopoulou S, Garipidou V, Athanassiou-Metaxa M, Harsoulis F (2007) Effect of zoledronic acid on markers of bone turnover and mineral density in osteoporotic patients with beta-thalassaemia. Ann Hematol 86:23–30
28. Voskaridou E, Christoulas D, Konstantinidou M, Tsiftsakis E, Alexakos P, Terpos E (2008) Continuous improvement of bone mineral density two years post zoledronic acid discontinuation in patients with thalassemia-induced osteoporosis: long-term follow-up of a randomized, placebo-controlled trial. Haematologica 93:1588–1590
29. Otrock ZK, Azar ST, Shamseddeen WA, Habr D, Inati A, Koussa S, Mahfouz RA, Taher AT (2006) Intravenous zoledronic acid treatment in thalassemia-induced osteoporosis: results of a phase II clinical trial. Ann Hematol 85:605–609
30. Piscitelli P, Auriemma R, Neglia C, Migliore A (2014) Alendronate: new formulations of an old and effective drug to improve adherence avoiding upper gastrointestinal side effects. Eur Rev Med Pharmacol Sci 18:3788–3796