

Original Article

**EFFECTS OF ZOLEDRONATE VERSUS PLACEBO ON SPINE BONE MINERAL DENSITY (BMD) AND MICROARCHITECTURE ASSESSED BY THE TRABECULAR BONE SCORE (TBS) IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS. A 3-YEAR STUDY<sup>†</sup>**

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## Abstract:

**Background and aim:** The Trabecular Bone Score (TBS) is an index of bone microarchitectural texture calculated from antero-posterior DXA scans of the lumbar spine (LS) that predicts fracture risk, independent of BMD. The aim of this study was to compare the effects of yearly intravenous zoledronate (ZOL) versus placebo (PLB) on LS BMD and TBS in postmenopausal women with osteoporosis.

**Materials and Methods:** Changes in TBS were assessed in the subset of 107 patients recruited at the Department of Osteoporosis of the University Hospital of Berne, Switzerland, who were included in the HORIZON trial. All subjects received adequate calcium and vitamin D3. In these patients randomly assigned to either ZOL (N=54) or PLB (N=53) during 3 years, BMD was measured by DXA and TBS assessed by TBS iNsight (v1.9) at baseline and 6, 12, 24, and 36 months after treatment initiation.

**Results:** Baseline characteristics (mean  $\pm$  SD) were similar between groups in terms of age,  $76.8 \pm 5.0$  years; BMI,  $24.5 \pm 3.6$  kg/m<sup>2</sup>; TBS  $1.178 \pm 0.1$  but for LS T-score (ZOL  $-2.9 \pm 1.5$  vs. PLB  $-2.1 \pm 1.5$ ). Changes in LS BMD were significantly greater with ZOL than with PLB at all-time points ( $p < 0.0001$  for all), reaching  $+9.58\%$  vs.  $+1.38\%$  at month 36. Change in TBS was significantly greater with ZOL than with PBO as of month 24, reaching  $+1.41$  vs.  $-0.49\%$  at month 36;  $p = 0.031$ , respectively. LS BMD and TBS were weakly correlated ( $r = 0.20$ ), and there were no correlations between changes in BMD and TBS from baseline at any visit.

**Conclusions:** In postmenopausal women with osteoporosis, once-yearly intravenous ZOL therapy significantly increased LS BMD relative to PLB over three years and TBS as of two years.

**Keywords:** OSTEOPOROSIS, Bone densitometry < QUANTITATION, Bisphosphonates < TREATMENTS

## INTRODUCTION

Over the past two decades, the significant burden of osteoporosis has been increasingly recognized, in terms of patient morbidity and mortality, health care utilization, and societal costs (1-5). Osteoporosis is a skeletal disease characterized by low bone mass and deterioration in bone micro-architecture that results in enhanced bone fragility and increased susceptibility to fractures (6). Bone mineral density (BMD) measured by dual X-ray absorptiometry (DXA), is the current reference standard for the diagnosis of osteoporosis (6-9). Fracture risk continuously increases with decreasing BMD, which is one of its strongest predictors (9-11). However, the greatest limitation of BMD measurement is that a considerable degree of overlap exists in BMD values between individuals with and those without subsequent fractures (12,13). This observation is witness to the fact that BMD is not the only structural determinant of bone strength. Trabecular bone microarchitecture, for example, also appears to be a significant determinant of bone strength, complementary to bone density (14,15).

The trabecular bone score (TBS) is a novel gray-level texture measurement that is based on the analysis of two-dimensional (2D) projection images that can be extracted from DXA images. The TBS is capable of differentiating between two 3-dimensional (3D) microarchitectures of cancellous bone that exhibit the same bone density but different trabecular characteristics (16,17). TBS values, as evaluated from 2D projection DXA images, demonstrate highly significant correlations with the 3D characteristics of trabecular bone microarchitecture, independent of BMD (16-18). A low TBS value has been found to be associated with degraded bone microarchitecture, low connectivity, high trabecular spacing, and a reduced number of trabeculae; conversely, a high TBS value has been found to be associated with good bone microarchitecture, including high connectivity, low trabecular spacing, and an augmented number of trabeculae (17,18). Hence, high values of TBS reflect strong, fracture-resistant

microarchitecture, while low TBS reflects weak, fracture-prone microarchitecture (16,17,19,20). Cancellous bone **microarchitectural texture** assessed by TBS was a predictor of osteoporotic fracture risk independent of spine and hip BMD in a retrospectively analyzed prospective cohort of 29,407 women, age 50 years or more, living in the Province of Manitoba, Canada. Furthermore, in this study, combining the TBS with BMD was superior to either TBS or BMD alone, with regard to fracture risk prediction (21).

Based on the positive results in several fracture endpoint trials, aminobisphosphonates have become the mainstay of antiresorptive treatment aimed at reducing the risk of vertebral and non-vertebral, including hip, fractures in postmenopausal women with osteoporosis (22-24). As such, yearly infusions of 5 mg of zoledronate (ZOL), a third-generation aminobisphosphonate, showed pronounced anti-fracture efficacy in the HORIZON fracture endpoint trial, producing significant reductions in new vertebral, non-vertebral, and hip fractures over a 3-year period in postmenopausal women with osteoporosis (24). This fracture risk reduction was consistent with improvements in BMD observed at the lumbar spine (LS) and the hip; but the order of magnitude of fracture risk reduction exceeded that expected from BMD changes alone (24,25). Micro-CT analyses of iliac crest bone biopsies performed in a subset of patients included in the HORIZON trial showed that patients treated with ZOL during 3 years had significantly higher trabecular bone volume and number of trabeculae, significantly lower trabecular separation, and numerically higher connectivity density, suggesting better preservation of trabecular structure with ZOL than with placebo (PLB) (26). These findings were consistent with observations performed in ovariectomized rats, which showed that decreases in trabecular architectural parameters were dose-dependently attenuated by ZOL and accompanied by dose-related improvements in bone strength parameters (27).

The effects of ZOL on the TBS, a non-invasive method for the *in situ* determination of intravertebral cancellous bone **microarchitectural texture**, are unknown. The aim of the present study was to compare the effects of yearly intravenous ZOL and PLB during 3 years, both on LS BMD and site-matched bone **microarchitectural texture** assessed by TBS.

## MATERIALS AND METHODS

The study was performed by retrospectively assessing DXA images to calculate TBS in the full subset of 107 postmenopausal women with osteoporosis recruited at the Department of the University Hospital of Berne, Switzerland, who were included in the HORIZON trial, a randomized, double-blind, placebo-controlled study comparing the effects of once-yearly intravenous ZOL and PLB over 3 years. All patients gave additional written informed consent to a local BMD sub study, which had been approved by the Cantonal Ethical Committee of Berne, Switzerland, as a local amendment to the protocol. TBS analysis was predefined and approved by the institutional board of the University Hospital of Berne, Switzerland.

### *Study population*

The HORIZON trial was a (1:1) randomized, double-blind, placebo-controlled clinical trial that compared the effects of once-yearly intravenous ZOL versus PLB in postmenopausal women with osteoporosis. In the original study, a total of 7765 patients were treated after random assignment to a once-yearly infusion over 15 minutes of either ZOL 5mg (N=3889) or PLB (N=3876) for a total length of follow-up of 3 years. All patients received adequate calcium and vitamin D3 supplementation. Major outcomes of the HORIZON trial were fracture incidence, change in BMD, and drug safety and tolerability. Full details on the HORIZON trial design and results were published earlier (24).

Patients included in the present study were the subset of all patients randomized and included in the HORIZON trial at the participating center of the Department of Osteoporosis of the

University Hospital of Berne, Switzerland, corresponding to **107** postmenopausal women with osteoporosis treated with either **ZOL (N=54) or PLB (N=53)** over 3 years.

### ***Measurement of trabecular bone score (TBS)***

DXA images (Hologic QDR 4500A<sup>TM</sup>, Hologic Inc., Bedford, MA) of the anteroposterior LS (L1-4) - collected at baseline, and at follow-up evaluations 6, 12, 24, and 36 months after the initiation of intravenous ZOL or PLB treatment - were sent to the Bone Disease Unit of the University Hospital of Lausanne, Switzerland, for blinded calculation of TBS values using TBS iNsight® Software version 1.9; Med-Imaps, Bordeaux, France. TBS was evaluated in the same regions of measurement as those used for the LS BMD, with TBS calculated as the mean value of the individual measurements for vertebrae L1-L4 from the original DXA scans, excluding any fractures **or degenerative changes**, in accordance with ISCD rules for individual vertebrae exclusion (**more than 1 standard deviation from immediately adjacent vertebrae**) (28). **As a result, in the PLB group, 30 patients with all vertebrae, 15 with 3 vertebrae, and 7 with 2 vertebrae were included with one patients being excluded because only one vertebra was assessable. In the ZOL group, 23 patients with all vertebrae, 26 with 3 vertebrae, and 4 with 2 vertebrae were included with 1 patient excluded because only one vertebra was assessable. The majority of the exclusions were related to degenerative changes in L4. All analyses were performed on the same vertebrae for both BMD and TBS parameters so that the results can be directly compared. Previously reported precision for TBS ranged between 1.48% (in house data) and 2.1% (21). At the Department of Osteoporosis of the University Hospital of Berne, the coefficient of variation for LS BMD measurements assessed in accordance with ISCD recommendations (15 outpatients representative of daily routine with triplicate measurements after repositioning) is 0.90% with a corresponding coefficient of variation of 1.12% for TBS. Thus, the Least Significant Change (LSC) is 2.49% for LS BMD and 3.10% for TBS.**

### *Statistical analysis*

After checking for normality distribution descriptive analysis included means and percentages with standard deviations. Change in BMD and TBS from baseline were calculated for each subject as the absolute change divided by the baseline value and converted into a percentage. Bivariate inter-group comparisons were performed using Student's t-test and Pearson's  $\chi^2$  analysis for continuous variables. Data were analyzed on an intention-to-treat basis. The threshold for statistical significance was set at  $p < 0.05$ ; and all inferential tests were two-tailed. All statistical analyses were performed using Stata (Version 12, StataCorp LP., Texas, USA).

## **RESULTS**

As shown in table 1, baseline characteristics (mean  $\pm$  SD) were similar between groups in terms of age,  $76.8 \pm 5.0$  years; BMI,  $24.5 \pm 3.6$  kg/m<sup>2</sup>; TBS  $1.178 \pm 0.1$  but for LS T-score (ZOL –  $2.9 \pm 1.5$  vs. PLB  $-2.1 \pm 1.5$ ;  $p=0.01$ ). These baseline characteristics were generally consistent with the mean values reported in the full population of the HORIZON trial (24).

**Because of exclusion, no show, or inability to retrieve the DXA scans, the number of subjects varied by visit, as shown in figure 1.**

As shown in table 2 and figure 1, changes in LS BMD were significantly greater with ZOL than with PLB at all time points (29), reaching  $+2.59\%$  vs.  $+0.04\%$  and  $+9.58\%$  vs.  $+1.38\%$  at months 6 and 36, respectively ( $p<0.0001$  for all). The change in TBS was of significantly larger magnitude with ZOL compared to PLB at month 24 ( $+1.11\%$  vs.  $-0.45\%$ ;  $p=0.049$ ) and month 36 ( $+1.41\%$  vs.  $-0.49\%$ ,  $p=0.031$ ). Compared to baseline, TBS increased significantly with ZOL at month 24 and 36 ( $+1.11\%$ ;  $p< 0.05$ , and  $+1.41\%$ ;  $p<0.04$ , respectively) but was not significantly different from baseline with PLB at any time point. TBS showed a slightly greater sensitivity than BMD (26 vs. 19%; McNemar-test  $p<0.6$ ) with regard to the proportion of patients below LSC in the PLB group. As expected, BMD

was more sensitive than TBS with regard to the proportion of patients achieving an increase above LSC in treated patients (96 vs. 35%;  $p < 0.001$ ).

Over three years, LS BMD and TBS were only weakly correlated ( $r = 0.20$ ); and there were no significant correlations between the change in BMD and TBS from baseline at any follow-up time point.

## DISCUSSION

In the present prospectively defined retrospective analysis of the full subset of women with postmenopausal osteoporosis randomized to once-yearly infusions of either ZOL or PLB in the HORIZON-study center of the Department of Osteoporosis of the University Hospital of Berne, Switzerland, ZOL induced a significantly larger sustained increase in LS BMD over 36 months and allowed for preservation of bone **microarchitectural texture** assessed by TBS at month 36. Furthermore, BMD and TBS were only weakly correlated.

TBS is a novel tool for fracture risk assessment in postmenopausal women (21). Its primary value beyond BMD is that it may specifically assess some dimensions of vertebral bone microarchitectural texture, which is recognized to be an important determinant of bone strength independent of BMD (12,14,30,31). **Several studies have demonstrated that TBS was strongly correlated with 3D micro-architecture parameters (such as Bone Volume / Trabecular Volume (BV/TV), Connectivity Density, Trabecular Number (TbN), Trabecular Thickness (TbTh), Trabecular Spacing (TbSp), Structure Model Index (SMI)) as assessed by using high resolution CT (93 microns) (17,18), micro CT (35 microns) (32). Correlations remained significant even at low resolution (33). Using TBS accurately differentiated between two 3D samples in which the amount of bone was identical, but characteristics differed with regard to TbN, TbTh, or TbSp (18). More recently, Roux et al.**



(32) compared the TBS with microarchitectural parameters measured using microCT with a 35- $\mu$ m isotropic resolution on lumbar vertebrae (L3) freshly harvested from 16 human donors. The TBS was significantly correlated to the BV/TV and the SMI (which reflects the rodlike versus platelike nature of the structure) with correlations coefficients of  $r=0.518$  ( $p=0.040$ ) and  $-0.597$  ( $p=0.015$ ), respectively. They concluded that TBS was significantly correlated to the most relevant microarchitectural parameters used to predict fracture risk (i.e.; BV/TV and SMI), might improve bone assessment in association with BMD using standard DXA, and could enhance fracture risk assessment without requiring  $\mu$ CT acquisitions in elderly patients. In summary, an elevated TBS reflects strong, fracture-resistant microarchitecture; a low TBS reflects weak, fracture-prone microarchitecture. TBS is therefore not a physical measurement but rather an index of the trabecular pattern of the measured bone strongly related to bone strength.

In the current study, we sought to establish whether TBS was useful for monitoring the effectiveness of anti-osteoporosis therapy beyond BMD within the context of a randomized clinical trial. In the subset of the patient population intended for BMD analysis in the initial HORIZON trial, the between group difference in LS BMD over 36 months measured by DXA was 7.0% ( $p<0.01$ ) (34) which is consistent with the between-group difference observed in the present analysis (8.20%,  $p<0.0001$ ). While BMD increased by 9.58% vs. baseline with ZOL over 3 years, TBS increased by only 1.41%, which corresponds to a change ratio of approximately 7. This finding is consistent with recent observations made in a retrospective analysis of the cohort included in the large provincial database in Manitoba, Canada, in which most of the women treated against osteoporosis used a bisphosphonate and in which the change in BMD over three years approximated 2% per year, versus 0.2% per year for TBS (35). Furthermore, in the present study, changes in BMD and in TBS were not correlated, supporting

the findings of previously-published research according to which the two parameters are measuring different characteristics of bone (21,35).

Once-yearly intravenous ZOL was shown to be significantly superior to PLB with regard to the reduction of vertebral and non-vertebral fracture risk, including at the hip (24,36). However, the order of magnitude of fracture risk reduction exceeded that expected from BMD changes alone (25,34). The analysis of iliac crest bone biopsies performed in a subset of HORIZON trial patients by micro-CT identified significantly better preservation of trabecular structure with ZOL than with PLB (26) and microspectroscopy analysis of these biopsies showed an increased mineral/matrix ratio with a larger proportion of younger bone tissue with ZOL compared with PLB (37). These findings suggest that ZOL may exert its fracture risk reduction effects by increasing bone mass and by preserving bone quality in terms of bone microarchitecture and bone material properties. These findings are consistent with the improvements in TBS vs. baseline observed with ZOL but not with PLB during 3 years.

**This study can be considered a first step towards establishing a possible role for TBS in the monitoring of osteoporosis therapy at the individual patient level, which would suppose known precision and least significant change (38). In the present study, the LSC was 3.1% for TBS, leading to 35% of treated patients being above LSC. Precision reported in this study is better than the generally reported precision for LS TBS reported in the literature which ranges from 1.5% to 2.1% (21). This difference may be explained by the stringent training received by all technicians as well as by the specific study procedures required by the HORIZON trial. Although 35% of treated patients showed a significant TBS increase consistent with a microarchitectural texture improvement, 65% remained below LSC such that the overall effects of ZOL on bone trabeculae can be considered as a preservation of vertebral microarchitectural texture in the majority of patients (35,39).**

Accepted Article

In several studies (16,19-21), TBS has been found: 1) to be lower in postmenopausal women with a past osteoporotic fracture relative to age- and BMD-matched women without fracture; 2) to, as it decreases, incrementally increase the odds ratio for spine fracture when combined with LS BMD; 3) to be lower in women with fractures, irrespective of whether their BMD meets the criteria for osteoporosis or osteopenia; 4) to prospectively predict fracture as well as LS BMD; and 5) to capture roughly one third of fractures misclassified using the BMD-dependent WHO definition of osteoporosis alone. **With this study being considered as a first step, further studies with other bone active substances, such as teriparatide, are needed to elucidate whether, and if so to what extent, the combination of BMD and TBS assessments may contribute to improve monitoring of osteoporosis treatment at the individual patient level.**

The present study has some limitations due to the retrospective nature of the analysis. However, the analysis was predefined and performed by intention to treat by persons blinded to treatment allocation and patient characteristics. The analysis was applied to the complete subset of a large population of postmenopausal women with osteoporosis included in a randomized, placebo-controlled trial by a single center. Finally, baseline characteristics of patients included in the present analysis were comparable to those of the full patient population included in the HORIZON trial. While the subset of **107** patients was large enough for comparing the effects of ZOL vs. PLB on TBS, it was not for establishing the predictive value of TBS alone or in combination with BMD with regard to fracture risk.

## CONCLUSIONS

In a prospectively defined retrospective analysis of a subset of postmenopausal women with osteoporosis included in the HORIZON fracture endpoint trial by a single center, once-yearly intravenous ZOL therapy **significantly increased LS BMD relative to PLB over three years and TBS as of two years.** Change in BMD and TBS were not correlated, confirming that TBS

reflects bone properties other than BMD, **more specifically bone microarchitectural texture.**

Further research is warranted to delineate the value of TBS as an index of treatment-related anti-fracture effects, as well as to explore the effects of other classes of bone active substances on TBS.

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**Table 1: Baseline characteristics (mean  $\pm$  SD)**

<b>Variable</b>	<b>ZOL (N=54)</b>	<b>PLB (N=53)</b>	<b>P value</b>
Age (years)	<b>76.6 <math>\pm</math> 4.8</b>	<b>77.0 <math>\pm</math> 5.2</b>	ns
Height (cm)	<b>157.8 <math>\pm</math> 6.3</b>	<b>156.7 <math>\pm</math> 4.8</b>	ns
Weight (kg)	<b>61.3 <math>\pm</math> 9.4</b>	<b>60.0 <math>\pm</math> 9.0</b>	ns
BMI (kg/m <sup>2</sup> )	<b>24.6 <math>\pm</math> 3.3</b>	<b>24.5 <math>\pm</math> 3.8</b>	ns
Lumbar spine TBS	<b>1.176 <math>\pm</math> 0.11</b>	<b>1.181 <math>\pm</math> 0.09</b>	ns
Lumbar spine T-score	<b>-2.9 <math>\pm</math> 1.5</b>	<b>-2.1 <math>\pm</math> 1.5</b>	<b>0.01</b>



**Table 2: Comparisons between lumbar spine BMD and TBS changes in ZOL vs. PLB treated women through 36 months follow-up (mean  $\pm$  SEM)**

month	Change from baseline <b>BMD</b>		P value PLB vs. ZOL	Change from baseline <b>TBS</b>		P value PLB vs. ZOL
	PLB	ZOL		PLB	ZOL	
0	<b>0%</b>	<b>0%</b>		<b>0%</b>	<b>0%</b>	
6	<b>+0.04% (<math>\pm</math> 0.5)</b>	<b>+2.59% (<math>\pm</math> 0.38)<sup>+</sup>*</b>	<b>&lt;0.0001</b>	<b>-0.66% (<math>\pm</math> 0.54)</b>	<b>-0.38% (<math>\pm</math> 0.49)</b>	<b>ns</b>
12	<b>+0.38% (<math>\pm</math> 0.6)</b>	<b>+4.96% (<math>\pm</math> 0.5)<sup>+</sup>*</b>	<b>&lt;0.0001</b>	<b>-0.36% (<math>\pm</math> 0.63)</b>	<b>+0.03% (<math>\pm</math> 0.69)</b>	<b>ns</b>
24	<b>+1.70% (<math>\pm</math> 0.7)*</b>	<b>+7.88% (<math>\pm</math> 0.5)<sup>+</sup>*</b>	<b>&lt;0.0001</b>	<b>-0.45% (<math>\pm</math> 0.68)</b>	<b>+1.11% (<math>\pm</math> 0.64)*</b>	<b>0.049</b>
36	<b>+1.38% (<math>\pm</math> 0.9)*</b>	<b>+9.58% (<math>\pm</math> 0.6)<sup>+</sup>*</b>	<b>&lt;0.0001</b>	<b>-0.49% (<math>\pm</math> 0.62)</b>	<b>+1.41% (<math>\pm</math> 0.79)*</b>	<b>0.031</b>

SEM = standard error of the mean

\* Significantly different from baseline  $p < 0.05$

<sup>+</sup> Significantly different from previous visit  $p < 0.05$

**Fig. 1:** BMD and TBS changes in ZOL vs. PLB treated women through 36 months of follow-up

