Archives of Osteoporosis (2019) 14:10
https://doi.org/10.1007/s11657-019-0561-x

SHORT SCIENTIFIC COMMUNICATION

Serum 25-hydroxy-vitamin D and the risk of fractures in the teriparatide versus risedronate VERO clinical trial

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Received: 28 August 2018 / Accepted: 7 January 2019

Abstract

Purpose Using data from the 2-year, randomized, double-dummy VERO trial, we examined the changes in 25-hydroxy-vitamin D (25[OH]D) concentrations over time, and whether the fracture risk reduction of teriparatide versus risedronate varies by baseline 25(OH)D sufficiency category.

Methods Postmenopausal women with established osteoporosis received subcutaneous daily teriparatide 20 μg or oral weekly risedronate 35 mg, with concomitant 500–1000 mg of elemental calcium and 400–800 IU/day of vitamin D supplements. Fracture endpoints were analyzed by predefined subgroups of 25(OH)D insufficient and sufficient patients. Heterogeneity of the treatment effect on fractures was investigated by logistic and Cox proportional hazards regression models.

Results At baseline, mean serum 25(OH)D was 31.9 ng/mL in the teriparatide group and 31.5 ng/mL in the risedronate group, and 16.8% and 17.9% of patients, respectively, were 25(OH)D insufficient. At month 6, the mean serum 25(OH)D concentration decreased in teriparatide-treated patients to 24.5 ng/mL (by approximately 23%) but remained relatively constant in risedronate-treated patients (32.2 ng/mL) ($p < 0.001$). Proportions of 25(OH)D insufficient patients at month 6 were 26.7% and 5.6%, respectively ($p < 0.001$). The risk reduction with teriparatide versus risedronate for any of the fracture endpoints did not significantly differ between subgroups by 25(OH)D sufficiency status at baseline, with nonsignificant ($p > 0.1$) treatment-by-25(OH)D interactions in all fracture analyses.

Conclusions Serum 25(OH)D concentration decreases during teriparatide treatment. Fracture risk reduction with teriparatide versus risedronate did not significantly differ between the two groups of patients defined by baseline 25(OH)D.

Trial registration ClinicalTrials.gov Identifier: NCT01709110
EudraCT Number: 2012-000123-41

Keywords Teriparatide · Fractures · Postmenopausal osteoporosis · 25-Hydroxy-vitamin D · Subgroup analysis · Bisphosphonates

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Published online: 18 January 2019

Introduction

The VERO (vertebral fracture treatment comparisons in osteoporotic women) trial was the first active-controlled, double-dummy, fracture endpoint study in postmenopausal women with established osteoporosis designed to compare the effects of the bone-forming drug teriparatide with those of the anti-resorptive risedronate on fracture risk as the primary study outcome [1]. Compared with risedronate-treated patients, teriparatide-treated patients of the VERO trial showed a 56% reduction in the risk of new morphometric vertebral fractures ($p < 0.001$), a 52% reduction in the risk of clinical fractures (clinical vertebral and non-vertebral fragility fractures; $p < 0.001$), and a 34% non-significant reduction in the risk of non-vertebral fragility fractures ($p = 0.1$). A predefined analysis of nine clinically relevant subgroups of the VERO trial revealed no evidence of heterogeneity of the treatment effect on fracture endpoints across the examined subgroups [2].

A previous analysis of the pivotal teriparatide, placebo-controlled "Fracture Prevention Trial," showed a high frequency of low 25-hydroxy-vitamin D (25[OH]D) levels in teriparatide-treated patients associated with normal or elevated concentrations of 1,25-dihydroxy-vitamin D (1,25[OH]2D) [3, 4]. There were no significant differences in the incidence of vertebral and non-vertebral fractures by baseline 25(OH)D concentrations in that study [3]. However, based on a retrospective study of 48 women with established osteoporosis treated with teriparatide who had previously received long-term therapy with bisphosphonates, Mok et al. suggested that the vitamin D status may influence the early anabolic effects of teriparatide evaluated by procollagen type 1 amino-terminal propeptide (P1NP) changes [5].

We examined the serum 25(OH)D status and its impact on the fracture incidence in the VERO trial by conducting a predefined subgroup analysis of the study's primary and key secondary fracture endpoints by subgroups of postmenopausal women with 25(OH)D sufficiency versus those with insufficiency at screening.

Methods

Study design

The VERO trial was an international, multicenter, randomized, double-blind, active-controlled, parallel-group, 24 months trial [1]. It included ambulatory postmenopausal women over 45 years of age with a bone mineral density T-score ≤ -1.5 standard deviations (SDs) at the femoral neck, total hip, or lumbar spine, and with radiographic evidence of at least two moderate or one severe prevalent vertebral fragility fracture according to the classification of Genant et al. [6]. Patients with serum 25(OH)D levels < 9.2 ng/mL (23 nmol/L) were excluded from the study, as well as patients with abnormally elevated values of serum intact parathyroid hormone (PTH) (1–84) at baseline defined as > 72 pg/mL (or > 7.6 pmol/L) and significantly impaired renal function as defined by a calculated endogenous creatinine clearance of < 30 mL/min/m^2. Further study entry criteria details have been reported by Kendler et al. [1].

A total of 1360 women were randomly assigned in a 1:1 ratio to receive either injectable subcutaneous teriparatide 20 μg daily plus an oral weekly placebo, or oral risedronate 35 mg weekly plus injectable subcutaneous daily placebo for up to 24 months.

Starting at the screening visit, all patients were to take approximately 500–1000 mg/day elemental calcium, depending on the dietary calcium intake as determined by the investigator, and approximately 400–800 IU/day of vitamin D throughout the entire duration of the study. The sponsor provided the calcium and vitamin D supplements to the study sites, but the brands varied across the different countries, because locally available, widely used preparations were preferred. Colecalciferol was the most frequently used vitamin D supplement metabolite (73.9% of the patients). Serum 25(OH)D levels were measured in all patients at screening, visit 3 (month 3), and visit 4 (month 6). The 25(OH)D concentration was evaluated by chemiluminescence immunoassay (DiaSorin LIAISON®). The intra-assay precision for the assay was 2.9 to 5.5% coefficient of variation (CV), and the inter-assay precision was 6.3 to 12.9% CV.

Statistical analysis

As defined in the statistical analysis plan for the VERO study [1], the treatment effect on fracture endpoints was evaluated for the subgroup of patients with 25(OH)D insufficiency (≥ 9.2 to < 20 ng/mL [≥ 23 to < 50 nmol/L]) and those with 25(OH)D sufficiency (≥ 20 ng/mL [≥ 50 nmol/L]) at baseline [7, 8], to examine if the treatment effect differs across these subgroups and to determine whether baseline 25(OH)D acts as a treatment effect modifier. This exploratory subgroup analysis was done for the primary and the key secondary fracture endpoints as defined in the statistical analysis plan of the study that was approved before study unblinding [1].

For the subgroup analysis of morphometric (radiographic) vertebral fracture endpoints, a logistic regression adjusted by treatment, baseline 25(OH)D category, treatment-by-baseline 25(OH)D category interaction, and the two stratification factors used at randomization (i.e., the antecedent of recent clinical vertebral fracture, and recent bisphosphonate use) was fitted. The modified full analysis set (mFAS) that included all randomized and treated patients with a baseline and at least one post-baseline spinal radiograph evaluable to assess the

vertebral fracture status at 24 months was used for these analyses.

The fracture endpoints within subgroups by baseline 25(OH)D category were analyzed using the same statistical methods as applied in the analysis of the VERO trial [1, 2]. Cochran-Mantel-Haenszel tests adjusted for the two stratification factors were employed to estimate the overall treatment effect between teriparatide and risedronate.

Subgroup analyses of non-vertebral and/or clinical vertebral fracture endpoints were done using a Cox proportional hazards regression model with the same covariates as specified above. The full analysis set (FAS) that included all randomized patients who received at least one dose of investigational product was used. The treatment-by-baseline 25(OH)D category interaction effect was tested at the significance level of 0.1. The risk ratios (for morphometric vertebral fractures) or the hazard ratios (for clinical fractures) with the associated 95% confidence intervals (CIs) and *p* values for teriparatide versus risedronate were presented in forest plots for each baseline 25(OH)D category and overall.

Serum 25(OH)D concentrations, the number of patients with 25(OH)D insufficiency, the daily dose of vitamin D, and the number of patients with supplemental vitamin D dose of 2000 IU/day were descriptively summarized by time point, as applicable. Mean serum 25(OH)D concentrations were compared between treatment groups using a mixed model for repeated measures, the number of patients with 25(OH)D insufficiency using Pearson chi-square test, and the mean and median daily vitamin D dose using *t* test and Wilcoxon rank sum test, respectively.

Results

In the VERO study, a total of 1360 patients were randomized and treated, 680 in each treatment group; 74.2% of patients overall completed the 24-month trial. Baseline demographics and clinical characteristics were similar between treatment groups as reported previously [1]. The overall patient population mean age was 72.1 years (range 45 to 93 years) and mean body mass index 27.0 kg/m^2 (SD 4.6 kg/m^2). At baseline, the mean (SD) serum 25(OH)D level was 31.9 (26.4) ng/mL in the teriparatide group and 31.5 (19.1) ng/mL in the risedronate group (Table 1); 114 patients (16.8%) in the teriparatide group compared with 119 (17.9%) in the risedronate group were 25(OH)D insufficient (serum 25(OH)D ≥ 9.2 and < 20 ng/mL).

Serum 25-hydroxy-vitamin D concentration and vitamin D supplement dose

After 3 and 6 months of study drug treatment and concomitant vitamin D supplementation, mean serum 25(OH)D concentrations had decreased in the teriparatide group but remained relatively constant in the risedronate group. At month 6, the mean (SD) serum 25(OH)D concentration was 24.5 (7.9) ng/mL in the teriparatide group compared with 32.2 (10.4) ng/mL in the risedronate group ($p < 0.001$ each at months 3 and 6; Table 1). At the same time, the number of patients with 25(OH)D insufficiency increased in the teriparatide group, to 153/572 patients (26.7%) at month 6, whereas it decreased in the risedronate group, to 33/591 (5.6%) at month 6 ($p < 0.001$ each at months 3 and 6; Table 1). Similarly, the proportion of patients with a shift from 25(OH)D sufficiency at baseline to insufficiency during the study was higher in the teriparatide group (19.0% at month 3 and 15.6% at month 6) than in the risedronate group (1.8% and 1.5%, respectively). Conversely, the proportions of patients with a shift from 25(OH)D insufficiency at baseline to sufficiency at the month 6 visit were 8.2% for patients receiving teriparatide and 12.1% for those receiving risedronate. Forty-two patients (6.2%) in the teriparatide group and 22 patients (3.2%) in the risedronate group remained 25(OH)D insufficient from baseline to the month 6 visit.

Slightly more teriparatide-treated patients (22 [3.2%]) than risedronate-treated patients (16 [2.4%]) took a supplemental dose of 2000 IU/day vitamin D starting at screening due to 25(OH)D insufficiency at screening ($p = 0.324$; Table 1). The mean (SD) daily dose of vitamin D was significantly ($p < 0.001$) higher in the teriparatide group (1408.4 [709.64] IU/day; median 1380.4 IU/day) than in the risedronate group (1206.4 [698.96] IU/day; median 900.0 IU/day).

Fracture risk reduction by baseline 25-hydroxy-vitamin D category

The risk reduction with teriparatide for new vertebral fractures did not significantly differ between patients with 25(OH)D sufficiency at baseline and those with 25(OH)D insufficiency. The risk ratio (95% CI) for the treatment comparison was 0.40 (0.25, 0.65) in patients with 25(OH)D sufficiency and 0.63 (0.24, 1.66) in patients with 25(OH)D insufficiency, leading to a non-significant ($p > 0.1$) treatment-by-baseline 25(OH)D category interaction (Fig. 1a).

Results for key secondary fracture endpoints were similar to those for the primary fracture endpoint. There was no indication that the 25(OH)D status at baseline significantly modified the fracture risk reduction of teriparatide versus risedronate, with all treatment-by-baseline 25(OH)D status interactions being non-significant for all the secondary fracture endpoints analyzed ($p > 0.1$) (Fig. 1b–e).

Generally, within the larger subgroup of patients with baseline 25(OH)D sufficiency, results were similar to those reported for the overall population [1], with a statistically significant fracture risk reduction with teriparatide versus risedronate for new vertebral fractures, pooled new and worsened vertebral

Table 1 Baseline characteristics, vitamin D dose, and serum 25-hydroxy-vitamin D levels (full analysis set)

Characteristics	Teriparatide ($N = 680$)	Risedronate ($N = 680$)	p value
Age, mean (SD)	72.6 (8.8)	71.6 (8.6)	–
Body mass index			
Number of patients with available data	678	678	
Mean (SD)	26.9 (4.6)	27.1 (4.6)	–
Daily dose of vitamin D (IU/day)			
Number of patients with dose available	677	676	
Mean (SD)	1408.4 (709.64)	1206.4 (698.96)	< 0.001[a]
Median (Q1, Q3)	1380.4 (800.0, 1796.0)	900.0 (800.0, 1602.4)	< 0.001[b]
Patients with supplemental vitamin D dose of 2000 IU/day starting at screening[c], *n* (%)	22 (3.2)	16 (2.4)	0.324[d]
Serum 25(OH)D concentrations, ng/mL, mean (SD)			
Baseline	31.9 (26.4)	31.5 (19.1)	
Month 3	23.8 (7.7)	31.9 (9.8)	< 0.001[e]
Month 6	24.5 (7.9)	32.2 (10.4)	< 0.001[e]
Patients with serum 25(OH)D ≥ 9.2 and < 20 ng/mL, *n*/*N* (%)			
Baseline	114/680 (16.8)	119/678 (17.6)	
Month 3	182/604 (30.1)	42/613 (6.9)	< 0.001[d]
Month 6	153/572 (26.7)	33/591 (5.6)	< 0.001[d]

To convert ng/mL to nmol/L for serum 25(OH)D concentrations, multiply by 2.5

25(OH)D 25-hydroxy-vitamin D, *N* total number of patients available, *n* number of patients in the specified category, *IU* international units, *Q1* first quartile, *Q3* third quartile, *SD* standard deviation

[a] *p* value from t test

[b] *p* value from Wilcoxon rank sum test

[c] As a result of a late protocol amendment when most study patients had already been randomized, patients with 25(OH)D concentration between 9.2 and < 20 ng/mL (23 to < 50 nmol/L) at screening were to be given a supplemental dose of vitamin D of 2000 IU/day

[d] *p* value from Pearson chi-squared test

[e] *p* value from a mixed model for repeated measures

fractures, and clinical fractures (Fig. 1a–c). In addition, the between-treatment difference for major non-vertebral fractures became statistically significant in favor of teriparatide (Fig. 1e). The sample size of the subgroup of patients with baseline 25(OH)D insufficiency was too small to show any significant treatment effect on fracture reduction.

Discussion

Our results from the VERO study confirm previously reported findings that treatment with teriparatide decreases the serum concentrations of the vitamin D metabolite 25(OH)D [4, 9]. After 3 and 6 months of study treatment, mean serum 25(OH)D concentrations were statistically significantly lower and proportions of patients with 25(OH)D insufficiency (serum 25(OH)D ≥ 9.2 and < 20 ng/mL) significantly higher in the teriparatide group than in the risedronate group, despite a higher mean daily dose of concomitant vitamin D supplements in teriparatide-treated patients. Cosman et al. suggested that due to the mechanism of action of teriparatide, i.e., the stimulation of 1α-hydroxylase, the conversion of 25(OH)D to the main biologically active metabolite 1,25(OH)2D is increased, resulting in a decrease of serum 25(OH)D but an increase of 1,25(OH)2D [4]. An alternative hypothesis for the reduction in 25(OH)D, not supported by data, is that it may be related to increases in fibroblast growth factor-23 (FGF-23) which has been shown to increase following treatment with teriparatide [10]. FGF-23 is a phosphaturic factor which also increases the degradation of 25(OH)D through 24-hydroxylation [11]. Finally, another potential but unproven explanation is that the increase in 1,25(OH)2D after teriparatide administration induces the CYP24A1 enzyme that catabolizes 25(OH)D to 24,25-dihydroxyvitamin D [12].

Recent studies suggest that assessing vitamin D status based on concentrations of 25(OH)D alone may be suboptimal to evaluate bone health [12]. It is unclear how well the serum concentration of 25(OH)D reflects the downstream effects of vitamin D receptor signaling in response to 1,25(OH)2D binding, as 25(OH)D may be activated, catabolized, or remain in an inactive form. Furthermore, assays for 25(OH)D are affected by concentration of vitamin D binding protein, which can vary between individuals, and may not reflect bioavailable 25(OH)D [13]. In fact, studies evaluating the relationship

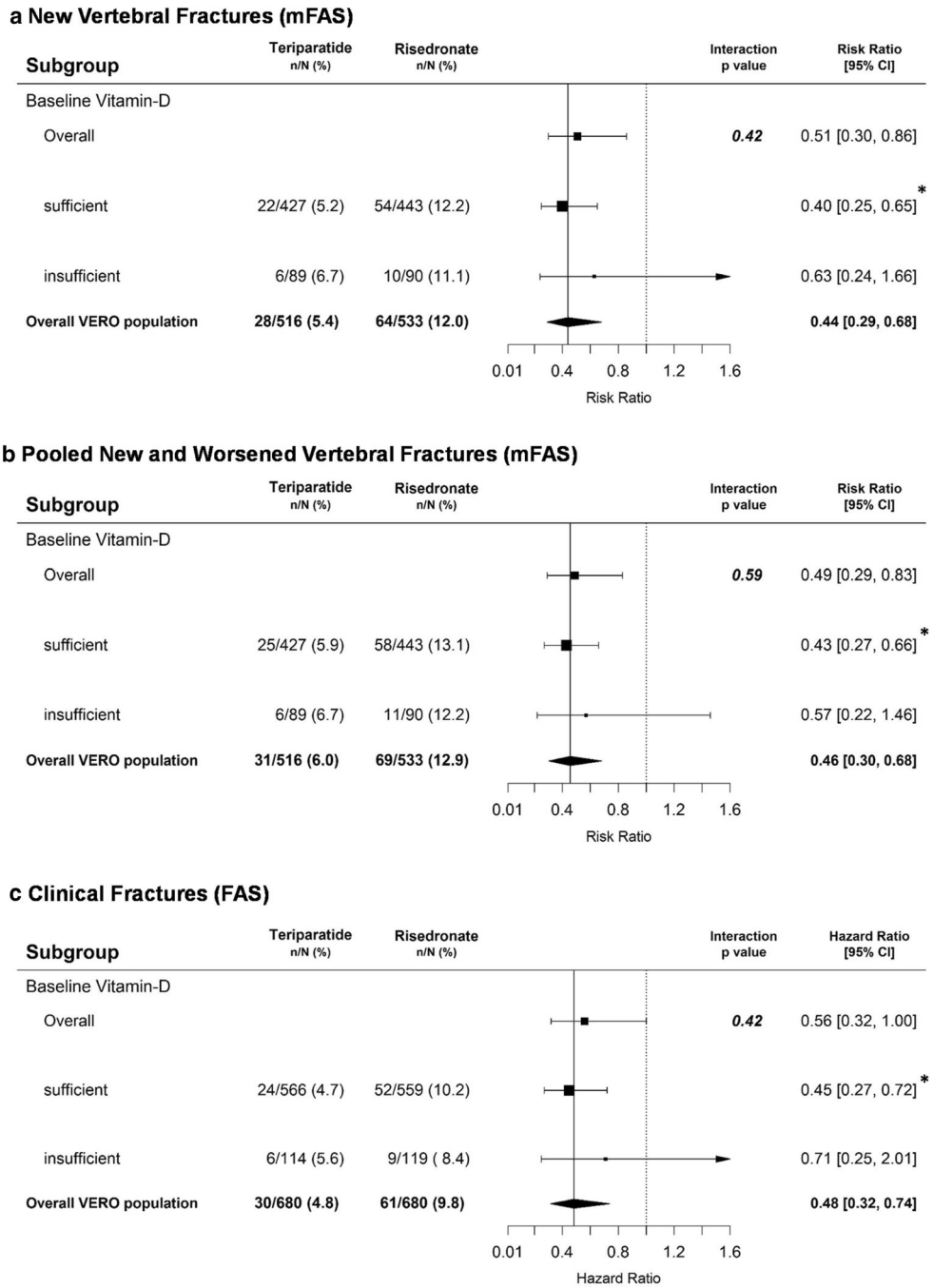

Fig. 1 Fracture risk reduction by 25-hydroxy-vitamin D baseline category. *CI* confidence interval, *FAS* full analysis set, *mFAS* modified full analysis set, *N* total number of patients available, *n* number of patients in the specified category. *$p < 0.001$; #$p = 0.08$. Notes: The mFAS included all randomized and treated patients with a baseline and post-baseline spinal radiograph evaluable after 24 months. The cumulative percentages are based on Kaplan-Meier analysis. Major non-vertebral fractures included hip, radius, humerus, ribs, pelvis, tibia, and femur (excluding pathologic fractures). For additional details on fracture definitions, see Kendler et al. [1]. **a** New vertebral fractures (mFAS). **b** Pooled new and worsened vertebral fractures (mFAS). **c** Clinical fractures (FAS). **d** Non-vertebral fragility fractures (FAS). **e** Major non-vertebral fragility fractures (FAS)

between 25(OH)D and bone density and fractures show mixed findings. Low 25(OH)D levels have been linked to the incidence of fractures in women in some studies [8, 14, 15], but not all [16–18]. For the most part, an increased fracture risk was observed with hip fractures and results were less consistent for non-hip fractures [19]. Although directly measuring 1,25(OH)2D, the active vitamin D hormone seems an appealing alternative, it has a lot of limitations and is currently not recommended. Circulating concentrations of 1,25(OH)2D are approximately 1000-fold lower than those of 25(OH)D [12]. Therefore, assays require significantly more serum, and extraction steps are required to account for interfering compounds. Moreover, 1,25(OH)2D has a half-life of only a few hours compared to weeks for 25(OH)D; thus, 1,25(OH)2D values are affected by renal function and may vary significantly from measurement to measurement [20].

Our findings in the VERO study support the limited value of baseline 25(OH)D to predict the fracture efficacy of teriparatide, at least when serum values are not extremely low since the cut-off level to enter the study was ≥ 9.2 ng/dL (23 nmol/L) and PTH concentrations had to be within normal limits. In the presented subgroup analyses of fracture endpoints in baseline 25(OH)D sufficient versus baseline 25(OH)D insufficient patients, the treatment-by-baseline

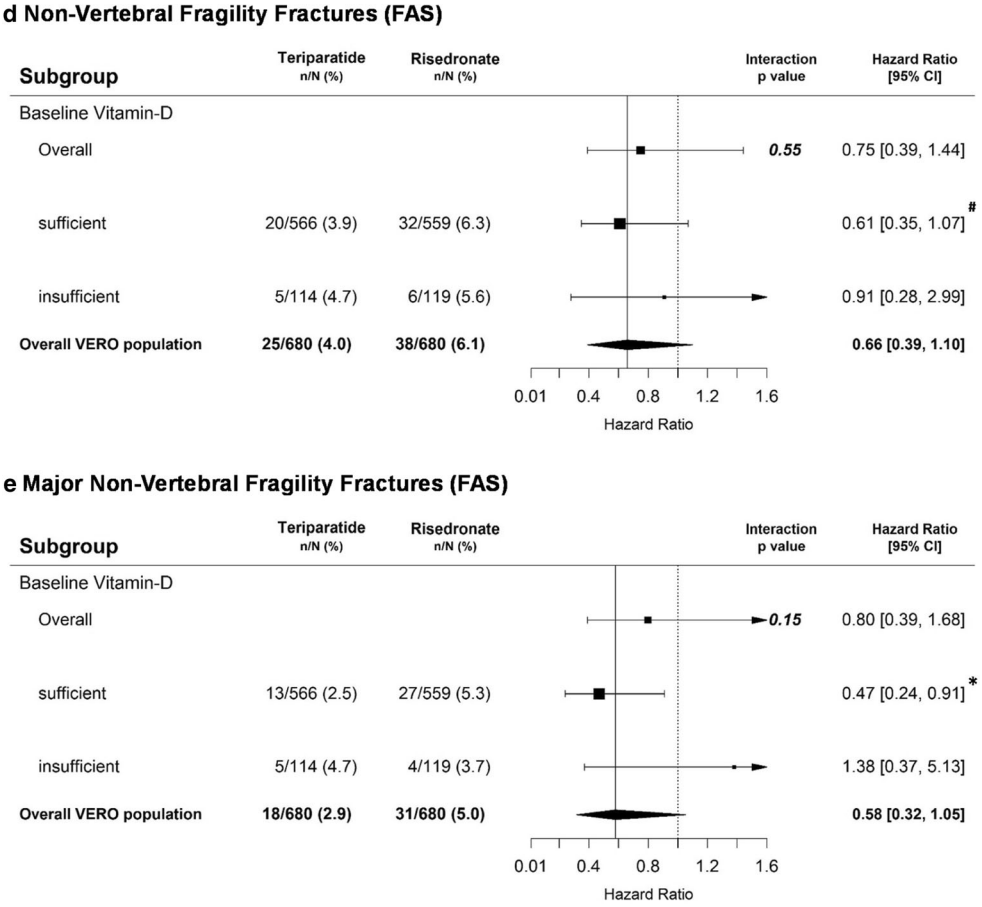

Fig. 1 (continued)

25(OH)D interaction was not statistically significant ($p > 0.1$) in any of the analyses. These results confirm previous findings in the placebo-controlled "Fracture Prevention Trial" which demonstrated that in postmenopausal women with osteoporosis, the response to teriparatide did not differ significantly between women with baseline 25(OH)D sufficiency and those with baseline 25(OH)D insufficiency [3]. Nevertheless, as in all patients with severe osteoporosis, ensuring adequate vitamin D supplementation is recommended.

Some limitations should be considered for the presented analysis. As is common for subgroup analyses, the statistical power to detect a treatment-by-subgroup interaction is limited due to the relatively small sample size of the study. This also led to the estimated CIs for the treatment effect within the subgroups being considerably wider than the corresponding CI estimated using the overall study population. Additionally, since patients with baseline serum 25(OH)D levels < 9.2 ng/mL (23 nmol/L) were excluded from the study, our findings only apply to patients having serum 25(OH)D levels above 9.2 ng/mL.

The strength of our analysis is that vitamin D supplementation in the trial was carefully monitored, and 25(OH)D serum levels were centrally measured. Moreover, the VERO study population is based on patients with a high fracture risk, a population that should be considered for osteoanabolic therapy. The VERO study was the first randomized clinical trial that assessed fractures as primary and key secondary efficacy endpoints, and thus, we were able to include in our analysis relevant clinical outcomes, such as clinical fractures, that have not been reported before in analyses by 25(OH)D sufficiency status.

In conclusion, fracture risk reduction with teriparatide versus risedronate did not significantly differ between women with baseline 25(OH)D sufficiency and those with 25(OH)D insufficiency, confirming previous findings of a placebo-controlled trial. Serum 25(OH)D levels decrease during teriparatide treatment, likely due to the increased conversion to 1,25(OH)2D. As in all patients with severe osteoporosis, an adequate supplementation with vitamin D is recommended during treatment with teriparatide, although monitoring of serum 25(OH)D may be limited to patients with very low 25(OH)D levels at baseline.

PRINCIPAL INVESTIGATORS The following investigators randomized at least one patient into the VERO study: **Argentina:** A. Alvarisqueta, A. Bagur, C. Gómez, L. Maffei, F. Massari; **Austria:** E. Boschitz, A. Fahrleitner-Pammer, G. Höfle, H. Koller, C. Muschitz, E. Preisinger; **Belgium:** I. Beyer, J.J.

Body, K. de Vlam, V. Gangji, P. Geusens, E. Gielen, S. Goemare, M. Leon, J.-Y. Reginster, M. Van den Berghe, R. Witvrouw; **Brazil:** J. Borges, M. Castro, L.A. Russo, C.A. Zerbini; **Canada:** J. Adachi, J.P. Brown, A. Cheung, S. Kaiser, A. Karaplis, D.L. Kendler, F. Morin, W. Olszynski, S. Seigel; **Czech Republic:** E. Dokoupilova, M. Ladova, R. Pikner, J. Stepan, V. Zikan; **France:** R. Chapurlat, J. Fulpin, C. Marcelli, M. Laroche, E. Lespessailles, T. Thomas; **Germany:** G. Dahmen, J. Fakler, I. Frieling, P. Hadji, R. Möricke, F. Thomasius, L. Unger, V. Ziller; **Greece:** M. Daniilidis, E. Foufoulas, G. Ioannidis, M. Kita, I. Kyrkos, I. Panagiotopoulos, S. Pnevmaticos; **Hungary:** E. Kanakaridu, K. Kudlak, P. Lakatos, K. Nagy, P. Somogyi, P. Suranyi, Z. Valkusz; **Italy:** G. Bianchi, M.L. Brandi, S. Giannini, G. Isaia, S. Minisola, G. Osella, M. Rossini; **Poland:** T. Blicharski, J. Brzezicki, P. Leszczynski, M. Mazurek, M. Rell-Bakalarska, J. Supronik; **Spain:** M.J. Amerigo, M. Bernad, E. Casado, N. Chozas, M. Díaz-Curiel, J. Malouf-Serra, J.A. Román, F.J. Tarazona; **USA and Puerto Rico:** N. Binkley, M. Bolognese, P. Bressler, M. Carroll, A. Chang, D. Cox, A. de la Llana, A. Dulgeroff, H. El-Kadi, M. Goldberg, S. Greenspan, H. Kenney, A. Kivitz, M.E. Lewiecki, M. Lillestol, P. Miller, A. Myers, P. Norwood, M. Perini, S. Rao, R.R. Recker, C.P. Recknor, H. Rodríguez, K.G. Saag, R. Sachson, C. Shuhart, O. Soto-Raíces, M. Spiegel.

Acknowledgments We are indebted to Anja Gentzel-Jorczyk (Clinical Trial Coordinator), and Estrella Crespo and Laura Briones (Data Management) for their contribution to the study, to Ansgar Dressler and Bhawna Basin from Trilogy Writing and Consulting for editorial assistance, to the members of the investigational teams at the study centers, and to the women who participated in the study.

Funding This VERO clinical trial was funded by Lilly.

Compliance with ethical standards

Conflicts of interest Salvatore Minisola: Speaker and/or consultant fees from: Abiogen, Amgen, DiaSorin, Lilly, Italfarmaco, Fujii, MSD, Takeda. Fernando Marin: Lilly Employee. David L. Kendler: Honoraria, research grants, and/or consultant fees from: Amgen, Lilly, AstraZeneca, Astellas, UCB. Piet Geusens: Research support, consultant and/or speaker fees from: Pfizer, Abbott, Lilly, Amgen, MSD, Roche, UCB, BMS, Novartis. Cristiano A.F. Zerbini: Research support from Lilly. Luis A. Russo: None. Enrique Casado: Speaker fees from: Amgen, Lilly. Astrid Fahrleitner-Pammer: Speaker fees from: Amgen, Alexion, BMS, Lilly, Fresenius. Jan J. Stepan: None. Eric Lespessailles: Speaker and consultant fees from: Amgen, Expanscience, Lilly, MSD; research grants from Abbvie, Amgen, Lilly, MSD, UCB. Rüdiger Möricke: None. Alicia Bagur: Speaker fees from Lilly and Craveri. Péter Lakatos: None. Pedro López-Romero: Lilly Employee. Jean Jacques Body: Speaker fee from Amgen; research support from Lilly.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Kendler DL, Marin F, Zerbini CAF, Russo LA, Greenspan SL, Zikan V, Bagur A, Malouf-Sierra J, Lakatos P, Fahrleitner-Pammer A, Lespessailles E, Minisola S, Body JJ, Geusens P, Möricke R, López-Romero P (2018) Effects of teriparatide and risedronate on new fractures in postmenopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet 391:230–240. https://doi.org/10.1016/S0140-6736(17)32137-2
2. Geusens P, Marin F, Kendler DL, Russo LA, Zerbini CAF, Minisola S, Body JJ, Lespessailles E, Greenspan SL, Bagur A, Stepan JJ, Lakatos P, Casado E, Moericke R, López-Romero P, Fahrleitner-Pammer A (2018) Effects of teriparatide compared with risedronate on the risk of fractures in subgroups of postmenopausal women with severe osteoporosis: the VERO trial. J Bone Miner Res 33(5):783–794. https://doi.org/10.1002/jbmr.3384
3. Dawson-Hughes B, Chen P, Krege JH (2007) Response to teriparatide in patients with baseline 25-hydroxyvitamin D insufficiency or sufficiency. J Clin Endocrinol Metab 92(12):4630–4636. https://doi.org/10.1210/jc.2007-0239
4. Cosman F, Dawson-Hughes B, Wan X, Krege JH (2012) Changes in vitamin D metabolites during teriparatide treatment. Bone 50(6):1368–1371. https://doi.org/10.1016/j.bone.2012.02.635
5. Mok J, Brown C, Moore AEB, Min SS, Hampson G (2018) Skeletal response to treatment with teriparatide (TPD) after bisphosphonate in post-menopausal women with osteoporosis and a high prevalence of secondary risk factors in real-life setting of a metabolic bone clinic; effect of age and vitamin D status. Endocr Res 13:1–8. https://doi.org/10.1080/07435800.2018.1454461
6. Genant HK, Wu CY, van Kuijk C, Nevitt MC (1993) Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 8(9):1137–1148. https://doi.org/10.1002/jbmr.5650080915
7. Institute of Medicine (US) Committee to review dietary reference intakes for vitamin D and calcium (2011) Dietary reference intakes for calcium and vitamin D. The National Academies Press, Washington DC, pp 260–262
8. Cauley JA, Greendale GA, Ruppert K, Lian Y, Randolph JF Jr, Lo JC, Burnett-Bowie SA, Finkelstein JS (2015) Serum 25 hydroxyvitamin D, bone mineral density and fracture risk across the menopause. J Clin Endocrinol Metab 100(5):2046–2054. https://doi.org/10.1210/jc.2014-4367
9. Licata AA (2005) Osteoporosis, teriparatide, and dosing of calcium and vitamin D. N Engl J Med 352(18):1930–1931. https://doi.org/10.1056/NEJM200505053521822
10. Sridharan M, Cheung J, Moore AE, Frost ML, Fraser WD, Fogelman I, Hampson G (2010) Circulating fibroblast growth factor-23 increases following intermittent parathyroid hormone (1-34) in postmenopausal osteoporosis: association with biomarker of bone formation. Calcif Tissue Int 87(5):398–405. https://doi.org/10.1007/s00223-010-9414-8
11. Alshayeb H, Showkat A, Wall BM, Gyamlani GG, David V, Quarles LD (2014) Activation of FGF-23 mediated vitamin D degradative pathways by cholecalciferol. J Clin Endocrinol Metab 99(10):E1830–E1837. https://doi.org/10.1210/jc.2014-1308
12. Ginsberg C, Katz R, de Boer IH, Kestenbaum BR, Chonchol M, Shlipak MG, Sarnak MJ, Hoofnagle AN, Rifkin DE, Garimella PS, Ix JH (2018) The 24,25 to 25-hydroxyvitamin D ratio and fracture risk in older adults: the cardiovascular health study. Bone 107:124–130. https://doi.org/10.1016/j.bone.2017.11.011

13. Powe CE, Ricciardi C, Berg AH, Erdenesanaa D, Collerone G, Ankers E, Wenger J, Karumanchi SA, Thadhani R, Bhan I (2011) Vitamin D-binding protein modifies the vitamin D-bone mineral density relationship. J Bone Miner Res 26(7):1609–1616. https://doi.org/10.1002/jbmr.387
14. Van Schoor NM, Visser M, Pluijm SM, Kuchuk N, Smit JH, Lips P (2008) Vitamin D deficiency as a risk factor for osteoporotic fractures. Bone 42(2):260–266. https://doi.org/10.1016/j.bone.2007.11.002
15. Gerdhem P, Ringsberg KA, Obrant KJ, Akesson K (2005) Association between 25-hydroxy vitamin D levels, physical activity, muscle strength and fractures in the prospective population-based OPRA study of elderly women. Osteoporos Int 16(11):1425–1431. https://doi.org/10.1007/s00198-005-1860-1
16. Cummings SR, Browner WS, Bauer D, Stone K, Ensrud K, Jamal S, Ettinger B (1998) Endogenous hormones and the risk of hip and vertebral fractures among older women. Study of osteoporotic fractures research group. N Engl J Med 339(11):733–738. https://doi.org/10.1056/NEJM199809103391104
17. Garnero P, Munoz F, Sornay-Rendu E, Delmas PD (2007) Associations of vitamin D status with bone mineral density, bone turnover, bone loss and fracture risk in healthy postmenopausal women. The OFELY study. Bone 40(3):716–722. https://doi.org/10.1016/j.bone.2006.09.026
18. Roddam AW, Neale R, Appleby P, Allen NE, Tipper S, Key TJ (2007) Association between plasma 25-hydroxyvitamin D levels and fracture risk: the EPIC-Oxford study. Am J Epidemiol 166(11):1327–1336. https://doi.org/10.1093/aje/kwm210
19. Looker AC, Mussolino ME (2008) Serum 25-hydroxyvitamin D and hip fracture risk in older U.S. white adults. J Bone Miner Res 23(1):143–150. https://doi.org/10.1359/jbmr.071003
20. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM; Endocrine Society (2011) Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 96(7):1911–1930. https://doi.org/10.1210/jc.2011-0385