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Zoledronic acid sequential to teriparatide may promote greater inhibition of bone resorption than zoledronic acid alone

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Abstract

Background: Teriparatide (TPTD) should be followed by an antiresorptive to maximize bone mineral density gain and anti-fracture protection. Infrequent zoledronic acid (ZOL) administration has demonstrated effectiveness. The duration of ZOL effect following TPTD is unknown.

Objective: To evaluate the effect of ZOL on bone resorption marker in a post-TPTD *versus* ZOL-alone scenario in osteoporotic patients.

Design: Retrospective cohort study.

Methods: Patients treated with TPTD followed by ZOL (TPTD–ZOL) or with a single ZOL infusion were identified in the database of a tertiary referral center. Clinical and laboratory data, including C-terminal telopeptide of type I collagen (CTX) following ZOL treatment, were compared.

Results: Twenty-six patients (93% women) treated with TPTD–ZOL and 41 with ZOL were comparable in age (median 70.1 *versus* 69.6 years, $p = 0.6$) and sex. Timing of CTX measurement post-ZOL was the same, median 1.0 year. CTX was lower following TPTD–ZOL (median 142.1 *versus* 184.2 pg/mL, $p = 0.005$). In a multivariable regression model (controlled for baseline characteristics), pretreatment with TPTD strongly predicted CTX <150 pg/mL, 1 year following ZOL (odds ratio = 7.5, 95% CI 1.3–58.1, $p = 0.03$). In a subgroup with sequential CTX measurements following one ZOL, significantly lower levels persisted in the TPTD–ZOL group for a median of 4.4 years follow-up.

Conclusion: ZOL-administered sequential to TPTD yielded deeper and more prolonged bone resorption suppression than ZOL alone. Prospective data are needed to confirm whether in a sequential treatment scenario, subsequent ZOL dosing interval should be less frequent.

Keywords: anabolic therapy, bisphosphonates, bone resorption, osteoporosis

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Introduction

The cycle of bone turnover is the core physiological process that ensures structural as well as metabolic bone health. Various medications for treating osteoporosis differ in their mode of action, specifically in their targeting different arms of the remodeling cycle.[1] The turnover process can be quantified by measuring bone turnover markers. The most widely used of these markers are N-terminal propeptide of type 1 procollagen (P1NP) and C-telopeptide of type 1 collagen (CTX), which reflect bone formation and resorption, respectively.[2]

Teriparatide (TPTD) is an anabolic agent that stimulates both bone formation and bone resorption, thus increasing bone turnover. Bisphosphonates suppress bone resorption and due to a coupling mechanism, bone formation as well, resulting in inhibition of bone turnover.[1]

It is well established that treatment with a bone forming agent should be followed by therapy with an antiresorptive agent.[3] Evidence suggests that treatment with bisphosphonates maintains the positive bone mineral density (BMD) effect and the anti-fracture efficacy generated by TPTD.[4,5]

The results of studies that explored the anabolic to antiresorptive treatment scenario,[6–8] and the reverse sequence[9] have led to the mainstay recommendation to favor anabolic-first, followed by an antiresorptive, especially in patients with a very high fracture risk.[10]

Zoledronic acid (ZOL) is a potent antiresorptive agent. Its antifracture efficacy was demonstrated in a pivotal study with a once-yearly administration.[11] More recently, less frequent administration has also been shown to prevent bone loss,[12] and even a single infusion promotes a sustained bone resorption inhibition effect.[13]

On one hand, it is the importance of the anabolic-antiresorptive scenario. On the other hand, ZOL administration tends to be less frequent. Taken together, the question arises as to the optimal frequency of ZOL administration in the sequence of an anabolic followed by an antiresorptive treatment. Whether pretreatment with TPTD influences bone turnover suppression induced by ZOL is currently unknown.

Study objectives

This study was designed to investigate the hypothesis that antiresorptive treatment with ZOL consequent to TPTD anabolic therapy promotes deeper bone turnover suppression, compared to ZOL therapy alone. The primary outcome was CTX measured 1-year post ZOL, given either as sequential to TPTD (TPTD–ZOL) or as a single treatment.

Methods

The bone metabolism database of our tertiary referral center was searched. Electronic medical records were screened for key words: 'teriparatide' and 'zoledronic acid', and their brand names. Patients treated with TPTD followed by ZOL, or with ZOL alone, were identified. The study period was from January 2008 to January 2022.

Retrieved data included demographic indices: age at ZOL treatment and gender. The clinical parameters retrieved included weight, height, prior fractures and prior treatment for osteoporosis, and factors that are known to affect bone health: smoking, glucocorticoid treatment, rheumatoid arthritis, plasma cell dyscrasias and primary hyperparathyroidism. Biochemical data included estimated glomerular filtration rate (eGFR) values, the vitamin D level closest to the ZOL treatment, and CTX levels. The latter were measured after a single ZOL infusion, either once or multiple times. CTX was measured with Cobas analyzer (Roche diagnostics). Pretreatment BMD results, as represented by lumbar spine and femoral neck *T* scores, were also retrieved.

We excluded from the analysis patients with primary hyperparathyroidism, with ongoing glucocorticoid treatment equivalent to 7.5 mg prednisolone daily or more, and those who received ZOL for skeletal dysplasia or Paget's disease. Additional exclusion criteria were the receipt of intravenous bisphosphonate less than 1 year before initiation of TPTD treatment, and treatment with TPTD for <1 year.

We excluded patients without CTX measurements, with CTX levels measured <6 months after ZOL infusion or with CTX values documented after multiple ZOL infusions.

A subset of patients treated with TPTD–ZOL or ZOL, and with serial CTX measurements after a single ZOL infusion, was identified and analyzed. The study was approved by an institutional review board.

Data analysis

We reported categorical variables as frequencies and percentages and used the chi square test to compare them. Non-normally distributed continuous variables were reported as medians and interquartile ranges (IQRs), and compared with the Mann–Whitney test.

We used multivariable logistic regression to estimate the odds ratio for low CTX (<150 pg/mL), controlling for confounders that were found significant in a univariable model (age, body mass index, kidney function, vitamin D level) or

Table 1. Characteristics of the patients treated with teriparatide followed by zoledronic acid (TPTD–ZOL), or ZOL alone.

Characteristic	Treated with TPTD–ZOL	Treated with ZOL alone	*p* Value
Patients	26	41	
Age at ZOL initiation, years	70.1 [63.6, 77.5]	69.6 [64.2, 76.2]	0.625
Sex			
Female	24 (92)	38 (93)	1
Male	2 (8)	3 (7)	
BMI, kg/m^2	25.5 [23.3, 28.0]	23.0 [21.0, 26.0]	0.065
eGFR, mL/min/1.73^2	83.7 [67.2, 98.5]	76.9 [68.9, 86.6]	0.401
Vitamin D (ng/mL)	32.0 [22.4, 37.9]	29.3 [28.0, 36.0]	0.879
Smokers	5 (19)	5 (12)	0.663
Rheumatoid arthritis	4 (15.4%)	1 (2.4%)	0.137
Glucocorticoids*			
Past treatment	4 (15.4%)	3 (7.3%)	0.42
Ongoing treatment	5 (19.2%)	1 (2.4%)	0.03
Baseline hip *T*-score	−2.1 [−2.6, −1.6]	−2.2 [−2.6, −1.6]	0.870
Baseline vertebrae *T*-score	−2.6 [−3.1, −2.0]	−2.4 [−3.1, −1.7]	0.516
Prior BP treatment	24 (92)	30 (73)	0.107
Duration of prior BP treatment, years	9.0 [6.0, 12.0]	5.0 [0.0, 9.6]	0.018
Prior fractures	22 (85)	20 (49)	0.007

Values are presented as number, median [interquartile range], or number (%).
*Patients with ongoing glucocorticoid treatment of 7.5 mg/day prednisolone or higher were excluded.
BP, bisphosphonate; CTX, C-telopeptide of type 1 collagen; eGFR, estimated glomerular filtration rate; TPT, teriparatide; ZOL, zoledronic acid.

clinically relevant (duration of prior bisphosphonate treatment).

A subset of patients with two or more CTX measurements following a single ZOL infusion was analyzed for median CTX, and the data are presented as box-plots.

All the statistical tests were two-sided, with $p < 0.05$ considered as statistically significant. We used the SPSS statistical software (IBM SPSS Statistics, version 28) and R version 4.1.0 (R Foundation for Statistical Computing) for statistical analyses.

Results

In total, 3052 files of osteoporosis patients were searched for relevant keywords – 'Zoledronic acid' and 'Teriparatide' or the equivalent commercial names. About 488 files were retrieved. After implementing exclusion criteria as mentioned above, data from 67 patients were collected. Of them, 26 were treated with a sequential protocol of TPTD followed by ZOL (TPTD–ZOL), and 41 were treated with ZOL alone (Table 1). TPTD was injected daily at a dose of 20 mcg, whereas ZOL acid was given as a single infusion at a dose of 5 mg.

Table 2. First CTX measurements post-zoledronic acid (post-ZOL) treatment, in patients treated with teriparatide followed by ZOL (TPTD–ZOL) or ZOL alone.

Characteristic	Treated with TPTD–ZOL	Treated with ZOL alone	*p* Value
Patients	26	41	
Timing of CTX measurement, post ZOL, years	1.0 [0.9, 1.1]	1.0 [0.9, 1.3]	0.563
CTX (pg/mL)	142.1 [91.7, 220.8]	184.2 [159.0, 262.0]	0.005
CTX ⩽150, first measurement, post ZOL	14 (54)	7 (17)	0.004

Values are presented as number, median [interquartile range], or number (%).
CTX, C-telopeptide of type 1 collagen.

The vast majority of patients were female: 92% and 93% in the TPTD–ZOL and ZOL groups, respectively ($p=1$). Median body mass index levels were 23 kg/m^2 (IQR 21, 26) in the TPTD–ZOL group, and 26 kg/m^2 (23, 28) in the ZOL group ($p=0.625$). For the respective groups, the median ages at initiation of ZOL therapy were 70.1 years (IQR 63.6, 77.5) and 69.6 (IQR 64.2, 76.2; $p=0.625$).

The median eGFR values were comparable in the TPTD–ZOL and ZOL groups: 83.7 mL/min/1.73^2 (IQR 67.2, 98.5) and 76.9 mL/min/1.73^2 (IQR 68.9, 86.6), respectively ($p=0.401$). The median vitamin D levels did not differ significantly between the groups: 29.3 ng/mL (IQR 28.0, 36.0) and 32.0 ng/mL (IQR 22.4, 37.9), respectively ($p=0.879$).

In the TPTD–ZOL compared to the ZOL group, the proportions of smokers (19% *versus* 12%, $p=0.663$) and persons with a history of rheumatoid arthritis (15% *versus* 2%, $p=0.137$) were higher, but neither of these differences reached statistical significance.

No patients in either sub-group were diagnosed with plasma cell dyscrasia.

Prior fractures were more common in the TPTD–ZOL than the ZOL group; 22 patients (85%) sustained fractures prior to TPTD treatment, compared to 20 patients (49%) in the ZOL group ($p=0.007$). The median vertebral *T*-score was lower in the TPTD–ZOL than the ZOL group: −2.6 (IQR −3.1, −2.0) *versus* −2.4 (IQR −3.1, −1.7), but this difference was not statistically significant ($p=0.516$). The median femoral neck *T*-scores were comparable in the two group: −2.1 (IQR −2.6, −1.6) and −2.2 (IQR −2.6, −1.6), respectively ($p=0.87$).

In the TPTD–ZOL group, 24 patients (92%) were previously treated with oral bisphosphonates, compared with 30 patients (73%) in the ZOL group ($p=0.107$). The median duration of prior treatment was longer in the TPTD–ZOL than in the ZOL group: 9 years (IQR 6, 12) *versus* 5 years (IQR 0, 9; $p=0.018$).

In the TPTD–ZOL group, 24 patients completed 2 years of TPTD treatment, one was treated for 21 and another for 12 months. The median time gap between completion of TPTD treatment and ZOL infusion was 0.14 years (IQR 0.05, 0.24).

Data were reviewed for side effects in both sub-groups. In the TPTD–ZOL group, two patients were reported to have mild hypercalcemia during treatment with TPTD, two additional patients had hypercalciuria. One patient reported headaches while another suffered leg pain. Following ZOL treatment in both groups, 15 patients had flu-like symptoms.

CTX levels post-ZOL were measured after a median of 1.01 years (IQR 0.92, 1.09) in the TPTD–ZOL group, and 1.02 years (IQR 0.94, 1.32) in the ZOL group ($p=0.563$; Table 2).

The median CTX level was lower in the TPTD–ZOL than the ZOL group: 142.1 pg/mL (IQR 91.7, 220.8) *versus*184.2 pg/mL (IQR 159.0, 262.0) ($p=0.005$; Table 2).

In the logistic regression model described above, pretreatment with TPTD was associated with a significantly higher risk of low (<150 pg/mL)

CTX level (odds ratio = 7.5, 95% CI 1.3–58.1, $p = 0.03$).

Following the first CTX measurement at 1 year after ZOL (presented in Table 2), a subset of 21 patients (9 in the TPTD–ZOL group and 12 in the ZOL group) who did not receive additional treatment, had second CTX measurements. These measurements were at a median of 2.5 [2.2, 2.8] and 2.3 [2.2, 2.8] ($p = 0.78$) years after ZOL treatment for the TPTD–ZOL and ZOL groups, respectively. Ten of these patients (5 in each group) had a third CTX measurement at 4.4 [3.5, 4.9] and 3.7 [3.4, 4.7] ($p = 0.84$) years, respectively, after the ZOL treatment. The medians of these second and third CTX measurements were lower in the TPTD–ZOL than the ZOL group: 95 [86–155] *versus* 218 [180–346], $p = 0.009$ and 133 [110, 140] *versus* 190 [157, 211], respectively, $p = 0.03$ (Figure 1).

Discussion

As anabolic agents for treating osteoporosis became available during the last two decades, the focus turned to the optimal treatment sequence. Antiresorptive therapy subsequent to anabolic treatment prompts greater improvement in BMD compared to antiresorptive therapy solely, and also more robust anti-fracture protection.[1] The updated recommendation is to favor anabolic medication followed by a bone resorption inhibitor for high-risk patients.[3,10]

TPTD exerts its anabolic effect *via* stimulation of bone remodeling.[14] Bone formation markers increase more rapidly and earlier during the course of therapy than do markers that reflect bone resorption, thus providing the so-called anabolic window. This may reflect the direct early anabolic effects of parathyroid hormone, which occur before the bone-remodeling cycle accelerates.[15]

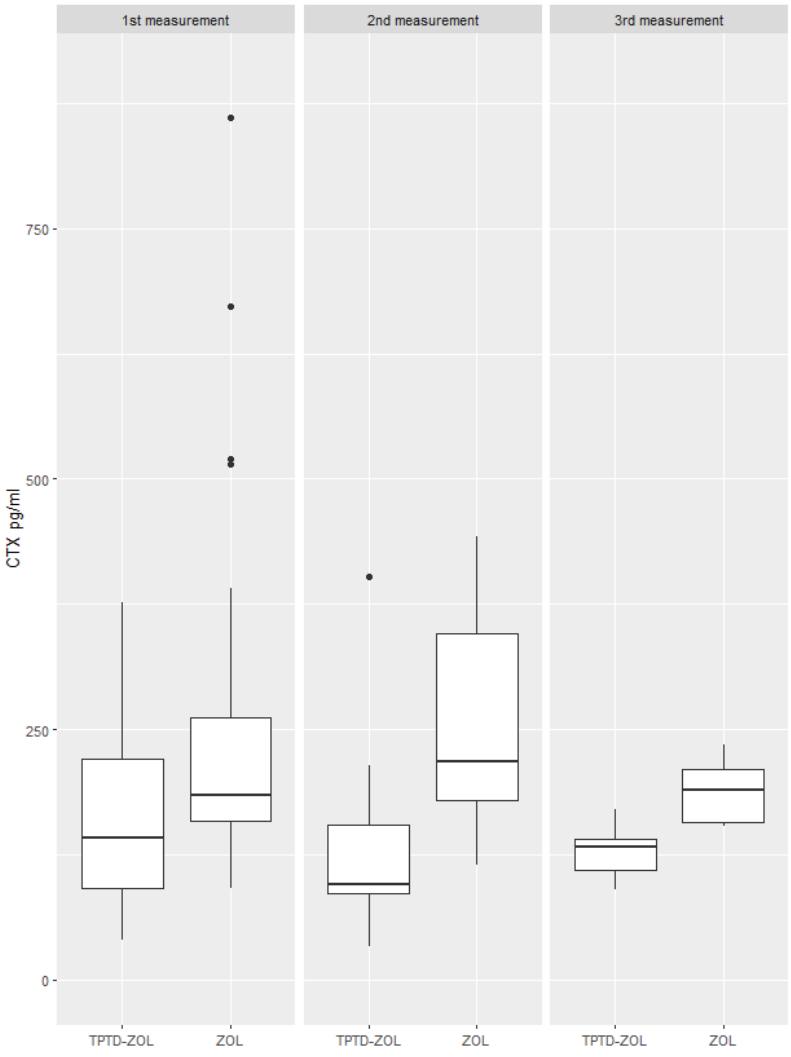
The optimal frequency of parenteral bisphosphonate therapy is a subject of ongoing research. The pharmacodynamics of this group of drugs is unique, as they remain in bone tissue well after incorporation into the bone, thereby retaining a prolonged effect.[16,17] Prolonged treatment poses cumulative dose and duration-related risks, namely atypical fractures and osteonecrosis of the jaw.[18] Over the past years, a lower frequency of treatment than the original 1-year interval was suggested.[13,19] Whether pretreatment with bone turnover-promoting medication should further modify the frequency of antiresorptive medication administered in a sequential scenario is not known. Specifically, the optimal dosing of ZOL following pretreatment with a bone anabolic agent has not been documented.

Our results suggest that ZOL administered sequential to TPTD promotes a deeper, persistent decline in serum resorption marker than ZOL alone.

Findings from several studies support an understanding that bisphosphonate therapy efficacy is dependent on baseline bone turnover.[20] Over 20 years ago, BMD gain with alendronate treatment was shown to be more pronounced in women with higher pretreatment bone turnover.[21] The same trend was observed with risedronate.[22] The mechanistic explanation was that bisphosphonate incorporation into the bone depends on the amount of active bone remodeling units. Specifically, higher turnover promotes bisphosphonate incorporation into the bone, resulting in a more pronounced BMD gain. In the fracture intervention trial, higher baseline bone turnover was linked to more robust alendronate-induced fracture protection,[20] while no such correlation was demonstrated with risedronate.[23]

We demonstrated that the probability of CTX decline below 150 pg/mL, 1 year after ZOL treatment, was significantly greater in patients treated with TPT and ZOL compared to ZOL alone. The cutoff of 150 pg/mL was selected for several reasons. The postulated target of bone turnover suppression under osteoporotic treatment is below the mean found in healthy young women, which in the Roche Cobas analyzer is quoted as 221 pg/mL, and the least significant change is 60 pg/mL.[24,25] Moreover, low CTX levels (<150 pg/mL) were shown, although inconsistently, to predict an increased risk of medication-related osteonecrosis of the jaw. This topic is under an unsolved dispute.[26,27]

In a small subset of our patients with serial CTX measurements following a single ZOL infusion, given either post-TPTD or alone, significantly lower CTX levels were demonstrated, up to a median 4.4 years of follow-up, in the sequential treatment scenario. Possibly, in the setting of the TPTD–ZOL treatment sequence, the subsequent



Number of patients	26	41	9	12	5	5
Time from ZOL, years	1.0 [0.9-1.1]	1.0 [0.9-1.3]	2.5 [2.2-2.8]	2.3 [2.2-2.8]	4.4 [3.5-4.9]	3.7 [3.4-4.7]
P-value for time-point difference	0.57		0.78		0.84	

Figure 1. Follow-up CTX levels are significantly lower in patients treated with teriparatide followed by zoledronic acid (TPTD–ZOL) than ZOL alone.
Values are presented as number, median [interquartile range].
TPTD, teriparatide; ZOL, zoledronic acid.

ZOL dosing interval might need to be modified accordingly.

Among our patients who were treated with TPTD and ZOL, compared to those treated with ZOL alone, a higher proportion was previously treated with oral bisphosphonates, and the duration of prior treatment was significantly longer. This is in concordance with a paradigm that advocates a stepwise approach to osteoporosis treatment, as reflected by a reimbursement policy that places TPTD mainly as a second-line option. We did not exclude from the analysis patients with prior oral treatments. This is because bone turnover markers (including CTX) rise rapidly following treatment with TPTD, regardless of prior

bisphosphonate exposure.[28] The length of prior treatment was not significant as an independent variable in the univariable logistic regression that examined the odds for CTX lower than 150 pg/mL Nevertheless, we included this variable in the multivariable analysis that demonstrated an impressive effect of TPTD pretreatment on low CTX 1 year after ZOL. A number of studies have shown that bone formation markers increase significantly in response to TPTD therapy, regardless of prior bisphosphonate therapy.[28–31] While increased BMD has also been demonstrated,[32] a mild difference was observed in BMD gain, between patients treated with bisphosphonate and those naïve to treatment.[33] Since we cannot definitely rule out the possibility of impact of prior bisphosphonate treatment on subsequent CTX levels, we conclude this as being a possibility, though unlikely.

Among our patients, prior fractures were more prominent in patients treated with TPTD, compared to ZOL alone. This is in accordance with local healthcare reimbursement criteria, which prioritize reimbursement for TPTD treatment in patients who sustain prior fractures. CTX can remain elevated up to 1 year following a fracture.[34] As CTX was measured 3 years (for TPTD–ZOL) or 1 year (for ZOL) after the treatment was commenced, prior fractures in our cohort were not expected to affect CTX levels.

Our study has several limitations. The small sample size and retrospective design preclude controlling for possible confounders and treatment allocation biases. Due to reimbursement constraints, P1NP levels were not measured on a regular basis as part of patient follow-up. Thus, we could not provide data regarding bone formation markers. We could not provide information on bone turnover prior to treatment initiation in either group, or during TPTD treatment among patients who received it. This information would be especially interesting due to the difference observed between the groups in prior bisphosphonate exposure. Throughout the study period (from 2008), bone turnover markers were used for individual decision-making (and have led to ZOL dosing-related decisions). This is contrary to a consensus approach that discouraged its use outside clinical trials.[35] The approach has been revised in recent years, and bone turnover markers are increasingly used in clinical practice.[36] Lastly, due to the small number of patients, we could not provide meaningful differences in fracture incidence between the groups.

In summary, this retrospective study confirmed our hypothesis that antiresorptive treatment with ZOL consequent to TPTD anabolic therapy promotes deeper bone turnover suppression, compared to ZOL therapy alone. Limited by the lack of data on anti-fracture efficacy due to the small retrospective design, and the mentioned limitations, we cannot conclude that in a sequential TPTD–ZOL treatment scheme, subsequent ZOL dosing interval might need to be modified, but we believe that prospective data generation to support this hypothesis is warranted.

Declarations

Ethics approval and consent to participate

This study was approved by the Chaim Sheba Medical center Helsinki Committee IRB 1917, IORG 1742, FWA 1580. Informed consent was waivered by the committee. 8858-21-SMC.

Consent for publication

All authors have given consent for publication.

Author contributions

Sharon Giveon: Data curation; Investigation; Writing – original draft; Writing – review & editing.

Galia Zacay: Formal analysis; Writing – original draft; Writing – review & editing.

Iris Vered: Data curation; Methodology; Writing – review & editing.

A. Joseph Foldes: Methodology; Writing – review & editing.

Liana Tripto-Shkolnik: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Data and material will be made available upon request.

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