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The Efficacy and Safety of 2-Year Treatment with Zoledronic Acid in Patients with Osteoporosis and the Influence of Previous Treatments in Actual Clinical Practice

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Abstract

Purpose: To investigate the efficacy and safety of treatment with zoledronic acid (ZOL).

Methods: Retrospective analyses were performed on patients with primary osteoporosis who received ZOL for 24 months. I analyzed some indicators, including changes in BMD (bone mineral density) until 24 months after the start of ZOL administration. Moreover, according to treatments prior to the administration of ZOL, patients were divided into 3 groups and all groups were analyzed. Patients who received ZOL after 18-month administration of 56.5-μg teriparatide formulation for once-weekly use (1/W-TPTD) were also analyzed.

Results: In 41 patients whose data were collected until 24 months after the start of ZOL administration, the lumbar spine BMD was significantly increased from baseline by 5.2% (3.6% - 6.9%) at 6 months after the start of ZOL administration, 6.8% (5.1% - 8.6%) at 12 months, 9.1% (7.3% - 11.0%) at 18 months, and 10.0% (8.1% - 11.9%) at 24 months. The femoral neck BMD was also significantly improved. Regarding previous treatments, the lumbar spine BMD and the femoral neck BMD was maintained/increased in each of 3 groups. In a group of patients who received ZOL after receiving treatment with 1/W-TPTD, ZOL administration significantly increased BMD further. A significant improvement was also observed in visual analog scale score of back pain, total Japanese Osteoporosis Quality of Life Questionnaire (JOQOL) score, and some individual JOQOL scores.

Conclusion: ZOL, which only needs to be administered once a year and has good compliance, can be a useful option for the treatment of osteoporosis.

Keywords: *Zoledronic Acid; Teriparatide; Osteoporosis; Bone Mineral Density; Born Turnover Marker*

Abbreviations

QOL: Quality of Life; BP: Bisphosphonates; BMD: Bone Mineral Density; ZOL: Zoledronic Acid; VAS: Visual Analogue Scale; ALN; Alendronic Acid; TPTD: Teriparatide; 1/W-TPTD: A Once-Weekly 56.5-μg Dose of Teriparatide Formulation; DXA: Dual Energy X-Ray Absorptiometry; P1NP: Type I Procollagen N-Terminal Propeptide; TRACP-5b: Tartrate-Resistant Acid Phosphatase-5b; JOQOL: Japanese Osteoporosis Quality of Life Questionnaire; D-TPTD: Once-Daily Teriparatide

Introduction

The treatment of osteoporosis aims to prevent fracture and maintain/improve bone health and QOL.

BP are excellent therapeutic drugs for osteoporosis that increase BMD and decrease the risk of fracture. In actual clinical practice, however, low adherence is one of the major issues in the management of osteoporosis. It is suggested that decreased rate of continuation and compliance may lead to lower effects. [1,2]. How to take BP is complicated. For example, since meals tend to influence oral BP potency, BP should be taken at the time of awakening when the stomach is empty, with a large volume of water to prevent gastrointestinal disorder caused by stimulating the digestive tract directly and after it was taken, a recumbent position should be avoided. Moreover, the absorption rate of BP is sometimes decreased by the beverage used to take BP [3] and the drugs taken concomitantly. Therefore, the effects that BP demonstrated during clinical studies may not be fully manifest in actual clinical practice. Once-yearly intravenous ZOL 5 mg formulation, which was introduced clinically in Japan in November 2016, is a BP that has a strong prolonged inhibitory effect on bone resorption and can be expected to improve adherence [4]. Therefore, this ZOL formulation avoids the above problems. In a phase 3 clinical study in Japan, it was reported that lumbar spine (L1-4) BMD, femoral neck BMD and proximal femur BMD were increased by 8.1%, 3.6%, and 3.3% by 24 months after the start of ZOL administration, respectively, and that the cumulative incidence of vertebral fractures and non-vertebral fractures decreased by 70% and 45%, respectively, over 2 years compared to placebo [5]. Therefore, ZOL is expected to exert similar effects in actual clinical practice.

In order to evaluate therapeutic effects on osteoporosis, not only the incidence of fractures and BMD but also back pain VAS and QOL are important indicators [6]. Improvement of lumbago, fewer days of lumbago, and fewer days of bed rest due to lumbago were reported from a study that analyzed the efficacy of 3-year use of ZOL for pain and QOL in postmenopausal women with osteoporosis [7]. Moreover, it has also been reported that ZOL significantly improved EQ-5D VAS scores after the surgical repair of hip fractures and decreased mortality [8] and that ZOL improved chronic lumbago associated with short-term Modic change [9]. Furthermore, in patients with osteoporosis who had a history of fracture, ZOL improved QOL significantly more than ALN [10].

Thus, in the present study, using data of patients who were treated with ZOL, I verified the efficacy and safety of ZOL in actual clinical practice, which are similar to those in clinical studies; analyzed the effects of ZOL on subjective evaluations such as pain and QOL evaluation, and demonstrated the influence of treatments prior to ZOL administration on the therapeutic effects of ZOL.

It has been reported that the use of bone resorption inhibitors such as BP and denosumab in maintenance therapy after ending TPTD administration, can prevent decrease in BMD that was increased by TPTD [11]. Our clinic also has many patients who are receiving maintenance therapy with ZOL after receiving TPTD. Therefore, I also analyzed the effects of sequential administration of ZOL on patients with a history of receiving 1/W-TPTD in our clinic.

Materials and Methods

Study design

The study was designed as a single-center, retrospective study in Japan. I included only the existing data into the analysis; no new data were collected. Therefore, I adopted an opt-out policy for use of the existing data. After review and approval by Japan Medical Association Ethical Review Board (approval number: R1-18), the research was conducted in accordance with the ethical principles of the Declaration of Helsinki, and the "Ethical Guideline for Clinical Research Involving Humans".

Study subjects

Patients with osteoporosis starting the treatment using ZOL from November 2016 to June 2019 at Koenji Orthopedics Clinic (Tokyo, Japan), who met the required inclusion criteria and did not meet the exclusion criteria were enrolled in this study.

Inclusion criteria

1. Patients 55 years of age or older.
2. Postmenopausal women who were diagnosed with primary osteoporosis.

Exclusion criteria

1. Patients with a metabolic bone disease other than osteoporosis.
2. Patients with a history of hypersensitivity to the study drug or BP.
3. Patients who have severe renal impairment (creatinine clearance < 35 mL/min) at the start.
4. Patients who are dehydrated (high fever, severe diarrhea and vomiting, etc.) at the start.
5. Patients who have hypocalcemia at the start.
6. Patients whom the physicians judged to be unsuitable because of idiosyncratic complications and markedly different background.

Evaluation

In this study, the efficacy assessment population included subjects whose data was obtained at all observation point. The safety assessment population included all subjects.

I evaluated the rate of change in the lumbar spine BMD and the femoral neck BMD. These parameters were measured by the DXA (Horizon C, Hologic, Inc., MA, USA). In addition, I evaluated the changes in P1NP, TRACP-5b, VAS score of back pain, JOQOL, which was developed by the Japanese Society for Bone and Mineral Research to measure the QOL of Japanese patients with osteoporosis and evaluates health-related QOL using 38 questions on a 152-point scale [12]. Various laboratory parameters were measured at baseline, 6, 12, 18 and 24 months after the start of ZOL administration.

The safety endpoint showed the number of cases and the incidence of adverse drug reaction observed within the 24 months after treatment. These were the incidence of acute phase response, the incidence of osteonecrosis of the jaw, and the incidence of other adverse drug reactions and changes in creatinine clearance, serum calcium level, serum phosphorus level and serum alkaline phosphatase level.

For the exploratory analysis, the following two items were evaluated.

1. According to treatments prior to the administration of ZOL, patients were divided into the BP group, 1/W-TPTD group and naïve group (patients who started ZOL without switching from other drugs). The rates of change in the lumbar spine BMD and femoral neck BMD in each group were analyzed 6, 12, 18 and 24 months after the start of ZOL. In this classification, no account was taken of vitamin preparations that had been used concomitantly before the start of ZOL.
2. Regarding patients who started ZOL immediately after 18-month use of 1/W-TPTD, the rates of change in the lumbar spine BMD and femoral neck BMD were analyzed at the start of 1/W-TPTD, 6 and 12 months after the start of 1/W-TPTD administration, at the start of ZOL (18 months after the start of 1/W-TPTD), and 6, 12, 18 and 24 months after the start of ZOL administration. Similarly, P1NP and TRACP-5b were analyzed.

Statistical analysis

The changes from baseline in each efficacy endpoint were assessed by using a paired t-test. Back pain VAS and JOQOL were assessed by using the Wilcoxon signed rank test.

For the analysis of each parameter, the patients with all measurement values between baseline and 24 months were included. The continuous variables of patient background were presented as the mean ± standard deviation. All other continuous variables were presented as the mean values (lower limit of the 95% confidence interval [CI] - upper limit of the 95% CI) and nominal scales were the number of patients (%). The significance level of test was 2-sided 5%. R software version 3.5.2 (R Core Team, Vienna, Austria) was used for statistical analysis.

Results

There were 88 subjects who met the inclusion criteria and did not violate the exclusion criteria of the present study. Among them, 69 subjects continued the study for 12 months after the start of ZOL and 41 subjects continued the study for 24 months.

Background and characteristics of the subjects at baseline are shown in table 1. In the present study, 49 subjects (55.7%) switched to ZOL from other drugs. Among them, 24 subjects (27.3%) previously received 1/W-TPTD, 13 subjects (14.8%) previously received BP, and 39 subjects (44.3%) received no therapeutic drug previously. Baseline values of the lumbar spine T score (L1-L4) and femoral neck *T* score were -1.76 ± 1.61 and -2.26 ± 0.59, respectively.

Item	Value	Item	Value
Age, yr	77.3 ± 7.0	Lumbar spine T score (L1-L4)	-1.76 ± 1.61
BMI, kg/m^2	22.5 ± 3.8	≤ -2.5	28 (31.8%)
With concomitant drug	74 (84.1%)	> -2.5	60 (68.2%)
VD3	63 (71.6%)	Femoral neck T score	-2.26 ± 0.59
VK	1 (1.1%)	≤ -2.5	31 (35.2%)
VD3+Ca	8 (9.1%)	> -2.5	57 (64.8%)
VD3+VK	2 (2.3%)	P1NP, ng/mL	55.3 ± 39.5
With previous therapeutic drug	49 (55.7%)	TRACP-5b, mU/dL	413.3 ± 179.9
BP	13 (14.8%)	ucOC, ng/mL	4.42 ± 3.11
1/W-TPTD	24 (27.3%)	CCr, mL/min	58.6 ± 16.5
Denosumab	7 (8.0%)	Ca, mg/dL	9.2 ± 0.4
Raloxifene	2 (2.3%)	P, mg/dL	3.4 ± 0.5
Romosozumab	3 (3.4%)	ALP, IU/mL	256.8 ± 123.0
With existing vertebral fracture	57 (64.8%)		
Number of vertebral fractures			
1	34 (38.6%)		
2	14 (15.9%)		
3 or more	9 (10.2%)		

Table 1: *Patient background data at baseline (N = 88).*

Values are presented as mean ± standard deviation or number (%).

BMI: Body Mass Index; VD3: Vitamin D3; VK: Vitamin K; Ca: Calcium; BP: Bisphosphonates; 1/W-TPTD: 56.5-μg Teriparatide Formulation for Once-Weekly Use; BMD: Bone Mineral Density; P1NP: Type I Procollagen N-Terminal Propeptide; TRACP-5b: Tartrate-Resistant Acid Phosphatase-5b; ucOC: Undercarboxylated Osteocalcin; CCr: Creatinine Clearance; P: Phosphorus; ALP: Alkaline Phosphatase.

The rate of change in the lumbar spine BMD was 5.2% (3.6% - 6.9%) at 6 months, 6.8% (5.1% - 8.6%) at 12 months, 9.1% (7.3% - 11.0%) at 18 months and 10.0% (8.1% - 11.9%) at 24 months, which represented a significant increase after 6 months. The rate of change in femoral neck BMD was 2.1% (0.8% - 3.5%) at 6 months, 3.5% (2.1% - 4.9%) at 12 months, 5.1% (3.2% - 7.0%) at 18 months, and 5.8% (4.1% - 7.6%) at 24 months, which represented a significant increase after 6 months. For the bone turnover markers, a significant decrease was observed in P1NP at 6 months and continued until 24 months (Figure 1c). TRACP-5b (Figure 1d) also showed a significant decrease like P1NP.

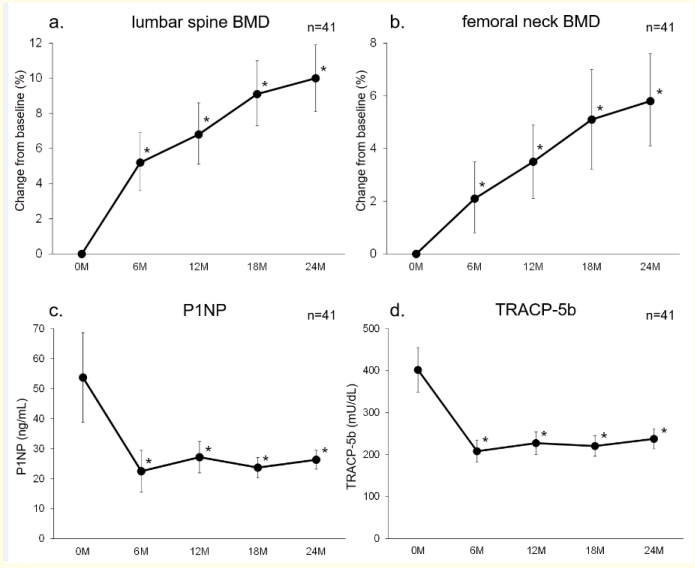


Figure 1: *The rate of change in (a) lumbar spine BMD and (b) femoral neck BMD and changes in (c) P1NP and (d) TRACP-5b. The values shown are the mean, and the error bars indicate the upper and lower limits of the 95% confidence interval. BMD, bone mineral density; P1NP, type I procollagen N-terminal propeptide; TRACP-5b, tartrate-resistant acid phosphatase-5b. *p < 0.05 vs.0-month, paired t-test.*

The rates of change in the lumbar spine BMD and femoral neck BMD attributed to a previous therapeutic drug are shown in figure 2a and 2b. The baseline value of the lumbar spine *T*-score was - 2.49 ± 1.33 in the BP group, -1.90 ± 1.58 in the 1/W-TPTD group, and -2.23 ± 1.79 in the naïve group, and the baseline value of the femoral neck *T*-score was -2.55 ± 0.25 in the BP group, -2.32 ± 0.55 in the 1/W-TPTD, and -2.42 ± 0.71 in the naïve group, showing no significant difference in baseline lumbar spine BMD or femoral neck BMD among the 3 groups. In the group naïve to treatment at the start of ZOL and the group treated previously with 1/W-TPTD, the lumbar spine BMD was significantly increased at 6 months and the increase continued to 24 months after the start of ZOL. The rate of change in the lumbar spine BMD in the naïve group was 6.3% (4.4% - 8.1%) 6 months later, 7.7% (5.3% - 10.1%) 12 months later, 10.4% (7.6% - 13.3%) 18 months later, and 12.4% (9.7% - 15.1%) 24 months later. The rate of change in the group previously treated with 1/W-TPTD was 5.3% (1.0% - 9.6%) 6 months later, 7.4% (3.6% - 11.2%) 12 months later, 8.2% (4.7% - 11.6%) 18 months later, and 8.7% (5.5% - 11.9%) 24 months later. In the group previously treated with BP, a significant increase was observed 18 months later. The rate of change in the group previously treated with BP was 2.9% (-1.1% - 6.8%) 6 months later, 2.5% (-1.2% - 6.2%) 12 months later, 6.7% (2.1% - 11.4%) 18 months later, and 3.9% (0.8% - 7.1%) 24 months later. The rate of change in the femoral neck BMD in the naïve group was 3.2% (1.0% - 5.4%) 6 months later, 5.1% (3.1% - 7.1%) 12 months later, 6.4% (3.4% - 9.5%) 18 months later, and 7.0% (4.1% - 9.9%) 24 months later. It was significantly increased at 6 months and the increase continued to 24 months after the start of ZOL. The rate of change in the group

previously treated with 1/W-TPTD was 1.3% (-1.2% - 3.8%) 6 months later, 2.4% (-0.1% - 4.9%) 12 months later, 4.7% (1.3% - 8.2%) 18 months later, and 5.5% (2.6% - 8.5%) 24 months later. It was significantly increased 18 and 24 months after the start of ZOL. The rate of change in the group previously treated with BP was -0.4% (-2.2% - 1.4%) 6 months later, -0.3% (-3.3% - 2.8%) 12 months later, 1.7% (-0.9% - 4.4%) 18 months later, and 2.6% (-1.1% - 6.3%) 24 months later. It showed no significant change.

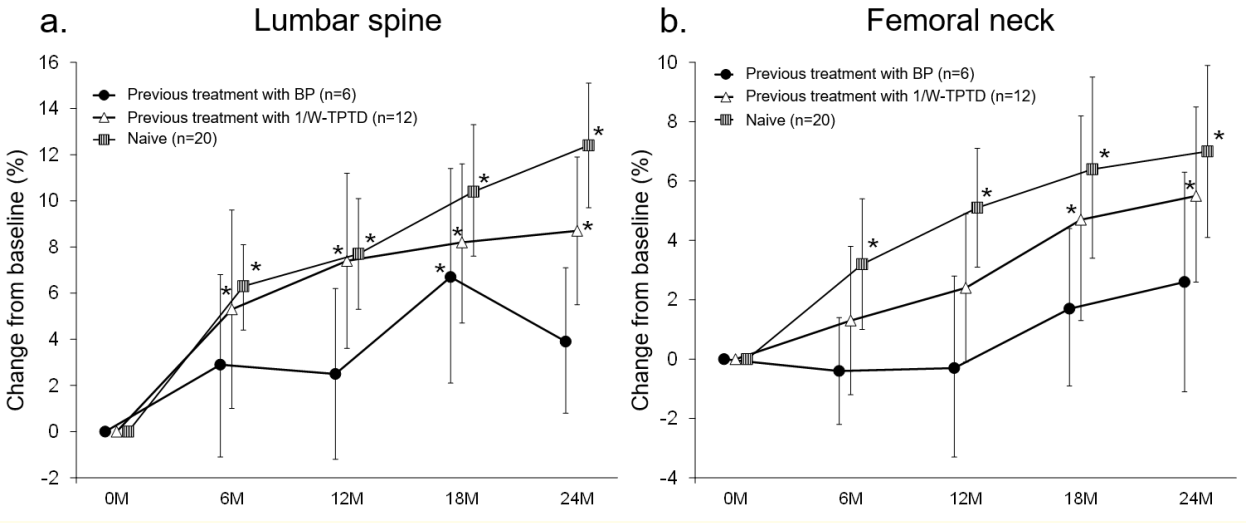


Figure 2: *The rate of change in (a) lumbar spine BMD and (b) femoral neck BMD produced by previous therapeutic drug. The values shown are the mean, and the error bars indicate the upper and lower limits of the 95% confidence interval. BMD, bone mineral density; BP, bisphosphonates; 1/W-TPTD, a 56.5-μg teriparatide formulation for once-weekly use.*

**p < 0.05 vs 0-month, paired t-test.*

Regarding change in the lumbar spine BMD in patients who received ZOL after 18-month treatment with 1/W-TPTD, although there was no significant difference after 18-month administration of 1/W-TPTD (at the start of ZOL) (P = 0.052), a significant increase was observed at all other time points compared to baseline. The baseline lumbar spine *T*-score was -1.93 ± 1.66. The rate of change in the lumbar spine BMD was 1.4% (0.3% - 2.6%) at 6 months, 2.3% (1.2% - 3.3%) at 12 months, 3.0% (-0.1% - 6.1%) at 18 months after the start of 1/W-TPTD administration (at the start of ZOL); 8.4% (3.0% - 13.8%) at 6 months, 11.7% (6.8% - 16.6%) at 12 months, 11.8% (6.8% - 16.9%) at 18 months and 12.3% (8.1% - 16.6%) at 24 months after the start of ZOL administration (Figure 3a). Regarding change in the femoral neck BMD, although there was no significant difference 6 months after the start of 1/W-TPTD administration or 18 months after the start of 1/W-TPTD administration (at the start of ZOL) (P = 0.744 and P = 0.390), a significant increase was observed at all other time points compared to baseline. The baseline femoral neck *T*-score was -2.41 ± 0.48. The rate of change in the femoral neck BMD was 0.9% (-1.9% - 3.7%) at 6 months, 2.6% (0.7% - 4.6%) at 12 months, 1.4% (-1.0 - 3.8%) at 18 months after the start of 1/W-TPTD administration (at the start of ZOL), 3.2% (0.8% - 5.7%) at 6 months, 4.3% (1.3% - 7.3%) at 12 months, 6.4% (2.6% - 10.2%) at 18 months, and 7.2% (3.9% - 10.5%) at 24 months after the start of ZOL administration (Figure 3b). P1NP increased when 1/W-TPTD was administered and then decreased when ZOL was started (Supplementary figure 1a). TRACP-5b consistently showed significant decreases compared to baseline (Supplementary figure 1b).

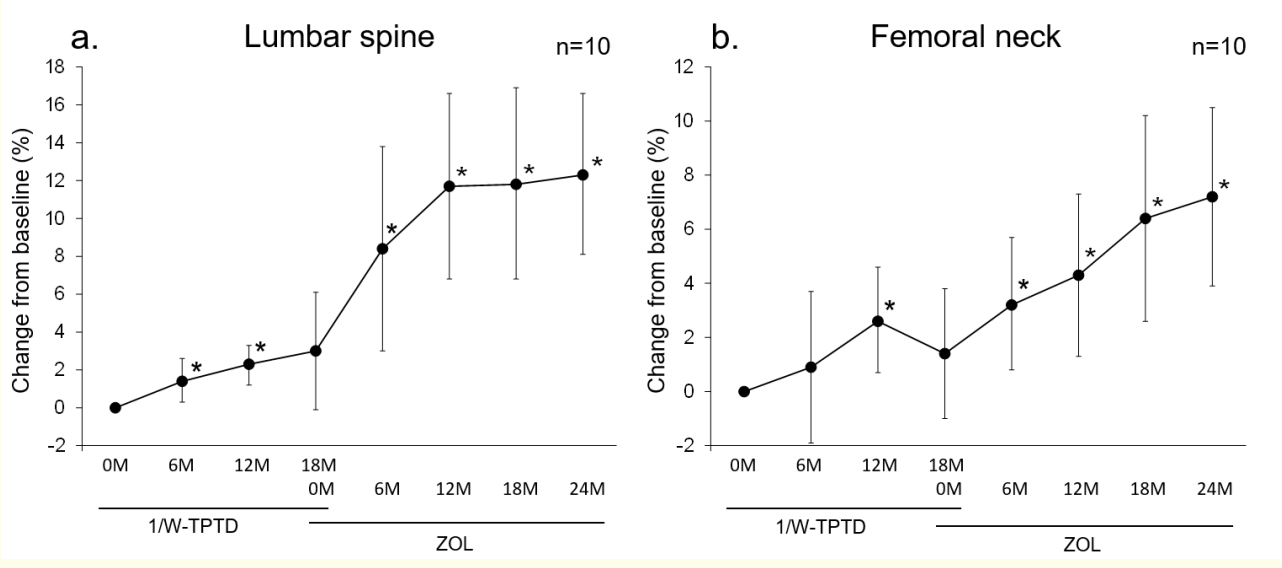
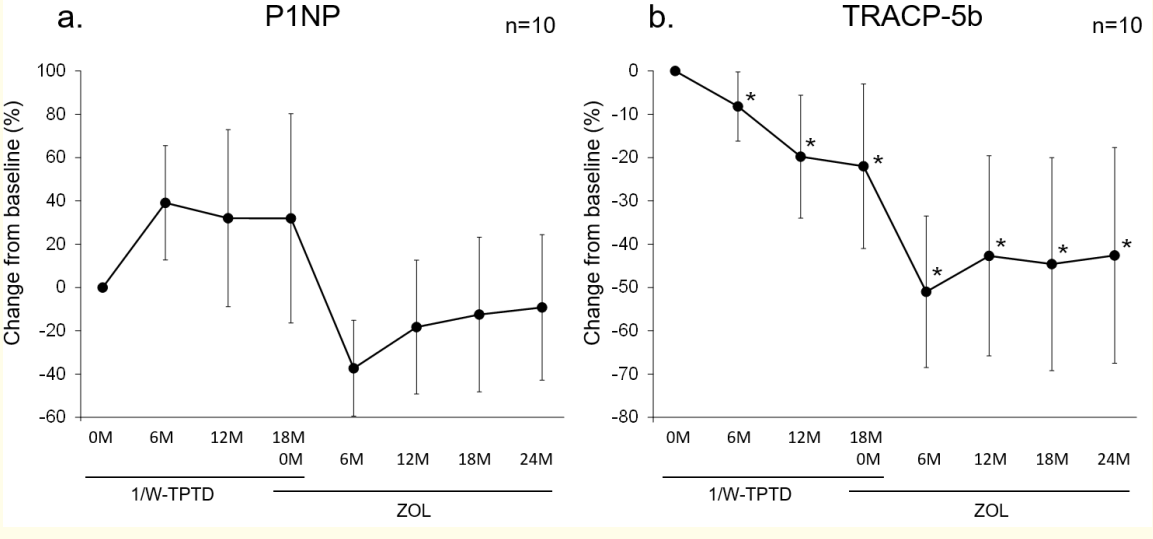


Figure 3: *The rate of change in (a) lumbar spine BMD and (b) femoral neck BMD during treatment with 1/W-TPTD and sequential Sadministration of ZOL. The values shown are the mean, and the error bars indicate the upper and lower limits of the 95% confidence interval. BMD, bone mineral density; 1/W-TPTD, a 56.5-μg teriparatide formulation for once-weekly use; ZOL, zoledronic acid.*

**p < 0.05 vs 0 month (1/W-TPTD), paired t-test.*



Supplementary Figure 1: *The rate of change in (a) P1NP and (b) TRACP-5b during treatment with 1/W-TPTD and sequential administration of ZOL. The values shown are the mean, and the error bars indicate the upper and lower limits of the 95% confidence interval. P1NP, type I procollagen N-terminal propeptide; TRACP-5b, tartrate-resistant acid phosphatase-5b, 1/W-TPTD, a 56.5-μg teriparatide formulation for once-weekly use; ZOL, zoledronic acid. *p < 0.05 vs 0 month (1/W-TPTD), paired t-test.*

Back pain VAS was 3.9 (2.7 - 5.0) at baseline and showed a significant decrease at all time points compared to baseline: 2.2 (1.3 - 3.1) 6 months later, 1.9 (1.0 - 2.9) 12 months later, 1.6 (0.6 - 2.6) 18 months later, and 1.4 (0.5 - 2.3) 24 months later (Figure 4).

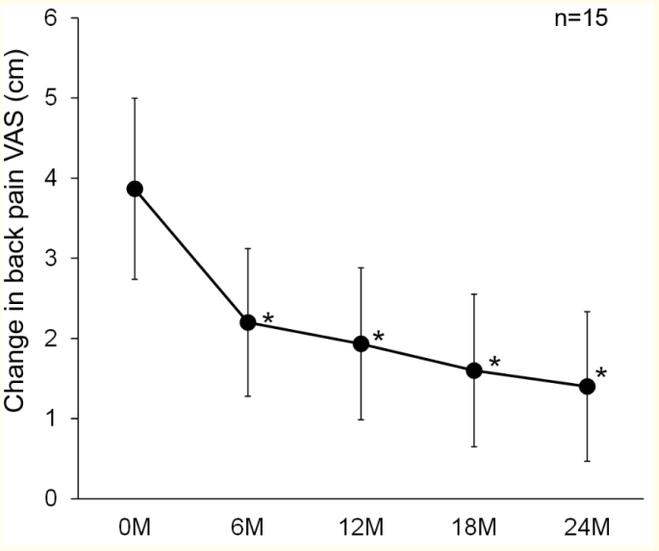


Figure 4: *Change in visual analogue scale (Back pain VAS).*
The values shown are the mean, and the error bars indicate the upper and lower limits of the 95% confidence interval.
**p < 0.05 vs 0 month, Wilcoxon signed rank test.*

Regarding JOQOL, the total score was 107.3 (101.1 - 113.6) at baseline and showed a significant improvement at all time points compared to baseline: 110.0 (103.8 - 116.2) 6 months later, 111.4 (105.2 - 117.7) 12 months later, 111.2 (105.0 - 117.4) 18 months later, and 111.7 (105.4 - 117.9) 24 months later. By domain, health perception was significantly improved from 6.0 (5.2 - 6.8) at baseline to 8.0 (7.4 - 8.7) 24 months later and falls/mental factors were significantly improved from 13.3 (12.3 - 14.2) at baseline to 13.7 (12.7 - 14.7) 24 months later (Figure 5).

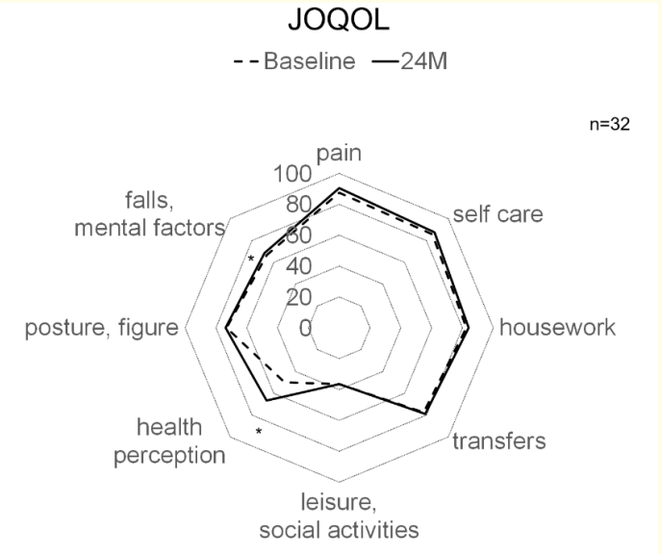


Figure 5: *Radar chart of 8 JOQOL domains at baseline and after 24-month treatment with ZOL.*
Mean values are shown. In this chart, the maximum point in each domain is set at 100. JOQOL, Japanese osteoporosis quality of life questionnaire.
**p < 0.05 vs 0 month, Wilcoxon signed rank test.*

The safety evaluation found that 18 subjects (20.5%) experienced adverse drug reactions, all of which were acute phase responses: pyrexia in 11 subjects (12.5%), myalgia in 11 subjects (12.5%), arthralgia in 3 subjects (3.4%) and lumbago in 2 subjects (2.3%). No osteonecrosis of the jaw occurred. None of the adverse drug reactions was serious, and the subjects recovered within 1 week. Creatinine clearance was significantly decreased 18 months later. However, serious renal impairment was not observed. The blood phosphorus concentration was significantly decreased 1 month later. However, the decrease was mild even when the blood phosphorus concentration was at the lowest level. There were significant decreases in blood calcium concentration 12 to 24 months later and alkaline phosphatase concentration 6 to 24 months later. However, both fluctuated within the reference range.

Discussion

In this study, significant increases in both lumbar spine BMD and femoral neck BMD were observed from 6 to 24 months after the start of ZOL administration. Previously, an 8.1% increase in the lumbar spine BMD from baseline and a 3.6% increase in the femoral neck BMD from baseline were reported from the ZONE study, which compared the effects of 24-month administration of ZOL with placebo [5]. In the present study, the lumbar spine BMD was increased by 10.0% from baseline and the femoral neck BMD was increased by 5.8% from baseline, demonstrating efficacy comparable to clinical trials. This result suggests that zoledronic acid exerts the expected efficacy in actual clinical practice with various patient backgrounds.

The bone turnover markers, P1NP and TRACP-5b, were decreased 6 months after the start of ZOL administration and remained low. TRACP-5b, a bone resorption marker, has been identified as an effect indicator that predicts increase in BMD due to treatment with ZOL [13] and in the present study, TRACP-5b remained low while BMD increased continuously. Therefore, the measurement/observation of TRACP-5b may be useful for predicting prognosis of BMD when ZOL is administered.

Regarding previous treatments that could conceivably have a large influence on therapeutic effects, my analysis was conducted in 3 groups (the naïve group, previous 1/W-TPTD treatment group, and previous BP treatment group, each of which contained at least 6 subjects). The results showed that in the naïve group and previous 1/W-TPTD treatment group, the lumbar spine BMD was significantly increased at all time points and the femoral neck BMD was also significantly increased at many time points. Thus, in the naïve group and the previous 1/W-TPTD treatment group, bone density was increased to a degree comparable to that observed in the clinical study [5], suggesting that expected effects can be achieved in actual clinical practice. 1/W-TPTD requires sequential BP treatment after its administration is ended. Since bone density was increased after the switch from 1/W-TPTD to ZOL, ZOL was viewed as suitable for sequential therapy after 1/W-TPTD.

In contrast, in the previous BP treatment group, the rate of increase was not as high as that in other groups. It has been reported that BP's effect reaches a plateau in 4 - 5 years [14,15]. In the present study, the duration of previous BP treatment was 5 years in 2 subjects, 3 years in 1 subject, 2 years in 2 subjects, and 1 year in 1 subject (data not shown), indicating many subjects had been treated with BP for a relatively long time. This conceivably contributed to the diminishing increase in bone density. Because ZOL can be expected to improve the continuation rate, compliance rate and bioavailability, and to have a strong inhibitory action on farnesyl pyrophosphate synthase (*in vitro*) [16], a high affinity to bone (*in vitro*) [17], etc., I think that switching to ZOL may be considered if treatment with other BP is not effective enough or taking oral BP is causing bothering patients.

Regarding changes in the lumbar spine BMD and femoral neck BMD during 18-month administration of 1/W-TPTD and sequential administration of ZOL, both lumbar spine BMD and femoral neck BMD were increased by the administration of 1/W-TPTD and then further increased by the administration of ZOL. The rate of increase in bone density due to 18-month administration of 1/W-TPTD in the present study was slower compared to that in the clinical study. A possible reason for this is the influence of BP use immediately before 1/W-TPTD in 6 out of 10 subjects who received sequential administration (data not shown). However, the administration of 1/W-TPTD conceivably not only increased bone density but also improved the structural and material properties of bone, restoring it to normal condition. Con-

ceivably, that is why a steady increase in BMD was observed when ZOL was administered subsequently. This effect was noticeable in the lumbar spine BMD and was also detectable in the femoral neck BMD. It is also suggested that replacing BP with 1/W-TPTD in patients who are being treated with BP, and in whom increase in bone density is diminishing, can increase poorly calcified new bone tissue, because of 1/W-TPTD-facilitated bone formation, and make these patients responsive to BP again.

There have been reports of sequential administration of TPTD and BP in this order. In patients who received maintenance therapy with ALN for 1 year after receiving D-TPTD for 1 year, increases in lumbar spine BMD and femoral neck BMD were maintained [18]. And among patients who received D-TPTD for the median of 20 months and then were followed up for a median of 30 months, maintenance therapy with BP further increased or maintained total hip BMD and femoral neck BMD that were increased at the end of D-TPTD administration [19]. This study is the first report to use 1/W-TPTD instead of D-TPTD and ZOL among BPs. In terms of improving compliance, it is notable that ZOL confers efficacy when administered only once a year as sequential therapy after 1/W-TPTD.

Back pain VAS was significantly improved 6 months after the start of ZOL administration, and this improvement was maintained until 24 months. That ZOL directly decreases back pain VAS is an unlikely mechanism for this improvement. However, Kawate., *et al*. reported that ALN improved joint pain VAS and JOQOL and suggested that improved VAS by ALN may be involved in QOL improvement [20]. Simultaneous improvement of pain VAS and QOL has been reported with denosumab, TPTD and other BP [21-24]. In the present study, JOQOL was significantly improved from baseline, 6 to 24 months later, suggesting that improved QOL resulted in improved back pain VAS. It has been reported that in localized bone lesions, increased inflammatory cytokines, prostaglandins, and growth factors cause bone pain by stimulating the activity of osteoclasts and nociceptors [25,26] and that BP reduced the osteoclast inducing cytokines [27,28], which as a result may provide pain relief.

Regarding safety, even subjects who developed acute phase responses did not become seriously ill, and suppressed values on renal function and other serological tests were recoverable and the acute phase responses were mild. In a phase 3 clinical study in Japan, the incidence of acute phase responses was 39.3% for pyrexia, 16.2% for arthralgia, 10.8% for myalgia and 6.3% for backache. In the present study, they were 12.5% for pyrexia, 12.5% for myalgia, 3.4% for arthralgia, and 2% for lumbago and less frequent than those in the clinical study. Although data about concomitant drugs other than those used to treat osteoporosis were not yet collected in the present study, patients with osteoporosis sometimes take antipyretic analgesics to control pain in actual clinical practice. Reports have indicated that acute phase responses due to ZOL are suppressed/reduced by the administration of acetaminophen or NSAIDs [29-31]. Therefore, acute phase responses in patients who are routinely taking antipyretic analgesics may be weakened. It is also known that the incidence of acute phase responses is decreased in patients with a previous history of BP use [32]. The present analysis included patients who had a history of BP use before the administration of ZOL, which may explain why the incidence of acute phase responses was lower than in the phase 3 clinical study, which excluded subjects who had a history of BP use within 2 years.

In the present study, 1 subject who concomitantly developed pyrexia and arthralgia due to acute phase response dropped out without continuation 12 months later, while other subjects are continuing, although a full 24 months of their data have not yet been collected. Because ZOL can be used without worry about forgetting to take it, I think compliance will be good if you pay attention to the acute reaction.

Although decreasing in other countries [33], the incidence of proximal femoral fracture continues to increase in Japan [34]. A possible reason is that low continuation rate of BP, which are the main therapeutic drugs for osteoporosis, reduces their expected effectiveness [1,2]. Fujimori., *et al*. reported that in Hokkaido, Japan, the 1-year BP continuation rate was 26.2% for once-daily BP and 39.0% for once-weekly BP [35], and Nakamura., *et al*. reported that the continuation rate for 1 or more years of once-weekly BP was 33% [36]. In other countries, it was reported that the proportion of patients who discontinued once-daily BP or once-weekly BP within 1 year was 20 - 30% [37] and the median time to discontinuation of once-daily ALN and once-weekly ALN was 2.8 years and 3.8 years, respectively [38]. The reasons for the longer duration of BP treatment in other countries than in Japan are unknown. Because the minimum of 1-year use is

needed for BP to prevent fracture [39], the relatively short duration in Japan may explain why the expected effect of BP is not fully realized. Since its therapeutic effects are maintained for 1 year by once-yearly administration, ZOL is beneficial for patients who are unable or unwilling to visit a hospital or take drugs regularly. ZOL is administered intravenously and does not require the patient's active participation. Therefore, I think ZOL can contribute to the improvement of adherence. On the basis of the results of the present study, I also think ZOL will increase bone density and even decrease fracture rate.

There are the limitations of the study. This study was conducted in single center. This is a retrospective study and did not consider patient demographics. In addition, the analysis in the study included patients with all data after 24 months.

Conclusion

In this study, ZOL exerted its expected effects in actual clinical practice in postmenopausal patients with primary osteoporosis. It significantly increased the lumbar spine BMD and femoral neck BMD and improved subjective evaluations such as back pain VAS and JOQOL. Moreover, ZOL was effective after 18-month treatment with 1/W-TPTD. All adverse drug reactions were acute reactions and were mild. In addition, all patients recovered within 1 week and most continued with ZOL. Only requiring administration once a year and showing good compliance, ZOL can be a useful treatment option for osteoporosis.

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Conflict of Interest

Fumitoshi Omura has received honorarium for lecture from Asahi Kasei Pharma Corporation. Fumitoshi Omura has not received any research grant directly, but Asahi Kasei Pharma Corporation has paid the research funding to outsourcers to support this study. However, the Asahi Kasei Pharma Corporation only provided funding and it was not involved in the management or analysis of this data.

Trial Registration Number

UMIN000042547.

Availability of Data and Material

Data are available on request to the author.

Author Contributions

Fumitoshi Omura: Original study design, formal analysis, writing.

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Volume 12 Issue 2 February 2021