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Persistence, Effects, and Adverse Events Associated with Real-World Daily Teriparatide Use in Japanese Patients with Osteoporosis

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Few studies have addressed the effects and adverse events associated with daily teriparatide use, as well as the adherence and causes for non-adherence, among Japanese patients with osteoporosis, particularly those older than 80 years. In this study, we aimed to clarify various parameters associated with daily teriparatide use in Japanese patients with osteoporosis in a real-world clinical setting. This retrospective study compared the persistence of daily teriparatide use and the associated effects and adverse events in older (≥80 years, n=52) and younger patients (<80 years, n=106) treated with teriparatide between May 2013 and May 2018 at a single orthopedic clinic. We observed a significantly higher treatment completion rate among younger patients compared to their older counterparts (59.6% *vs*. 40.6%, p=0.036). Of the 74 patients (both patient groups) who completed a 24-month treatment course, only one (1.35%) developed new vertebral fractures. Our findings suggest that older patients would benefit from consistent osteoporosis treatment, particularly with a generally safe and effective agent, such as teriparatide. However, Log-rank test also shows the older patients exhibits a greater tendency to drop out than the younger patients (p=0.0238). The older patients tended to continue to drop out from the beginning. Accordingly, our results emphasize the importance of interventions, especially continuous encouraging from the first self-injection of teriparatide.

Key words osteoporosis, old-old, first injection, fracture, adverse event

INTRODUCTION

Japan's ageing population is an increasing problem because members of the generation post-baby boom will be older than 75 years in 2025.[1)] This rapid aging is supposed to increase further medical expenses nationwide.[1)] Although Japanese women have the longest life expectancy worldwide, their relative healthy life expectancy is approximately 12 years shorter.[2)] Consequently, it is important to extend this healthy life expectancy.

In older people, bone fractures can lead to disability and cause patients to become bedridden. The majority of osteoporotic fractures (>85%) are caused by falls.[3)] These osteoporotic fractures comprise a major public health burden in super-aging societies, such as Japan, and are associated with increased patient morbidity and mortality rates, as well as higher medical expenses.[4)] Therefore, the early detection of reduced bone density and treatment of osteoporosis are important.

According to JAPOR, adherence refers to to the degree or extent of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency. And, Medication persistence refers to the act of continuing the treatment for the prescribed duration.[5)] In the clinical studies of daily Teriparatide, medical persistent or adherence have been evaluated. The persistent use of medications for osteoporosis has been associated with a reduced risk of fracture and significant reductions in total healthcare costs.[6)] Furthermore, the prevention of disabling osteoporotic fractures can enable older people to retain their independence and, consequently, their self-esteem. Taken together, these strategies support a healthy life expectancy. Despite their advantages, medications for osteoporosis are associated with low adherence; for example, one study found that 45.2% of patients had stopped filling their prescriptions one year after beginning treatment for osteoporosis.[7)]

Teriparatide (recombinant human parathyroid hormone) is an anabolic agent that promotes bone formation and, thus, increases bone density in the spine and femur. This agent is recommended for the treatment of patients with a high risk of fracture, as well as those who face an increasing risk of fracture, despite treatment with a bisphosphonate or selective estrogen receptor modulators.[8,9)] However, the effectiveness of and adverse events related to daily teriparatide use, as well as the treatment cessation rate and associated causes, have rarely been investigated in Japanese patients with osteoporosis, particularly those older than 80 years.

Older people usually visit a local community clinic, rather than a core hospital, when they first observe bodily pain. However, most clinical studies and trials are conducted in core hospital settings. To address this gap in research, we conducted a study at a local orthopedic clinic where many area resi-

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dents seek consultation for low back pain or fracture. In this real-world clinical study, we aimed to evaluate the persistence, effects, and adverse events associated with daily teriparatide use in Japanese patients with osteoporosis.

MATERIALS AND METHODS

Participants This study included all patients who were prescribed teriparatide 20 μg once daily via subcutaneous injection at a single orthopedic clinic between May 2013 and May 2018. Patients whose data were not available were excluded. Although individuals older than 75 years are commonly described as "old-old" in Japan, patients included in our study had an average age of 81.3 ± 5.2 (range, 67-95) years. As this average was higher than the mean age (75.4 years) of patients reported in The Last Specific use survey: Safety Summary, we divided our subjects into two age groups: Group A, <80 years; and Group B, ≥80 years.[10]

This retrospective study was conducted in accordance with the 1964 Declaration of Helsinki and subsequent revisions. Informed consent was obtained from all patients using the opt-out method of the clinic. The Ethics Committee for Clinical Research of Pharmaceutical Sciences of Osaka University approved this study (approval number: yakuhito 29-15).

Measurements For all patients who met the inclusion criteria, we retrospectively reviewed the medical records for laboratory test values measured within 3 months before and after the prescription of teriparatide.

The following items were surveyed: age, sex, height, weight, body mass index (BMI), concomitant rheumatoid arthritis (RA), corticosteroid use, estimated glomerular filtration rate (eGFR), type I procollagen N-terminal propeptide (P1NP) level, tartrate-resistant acid phosphatase-5b (TRACP-5b) level, total hip bone mineral density (BMD), femoral neck BMD, lumbar spine (L2–4) BMD, and trabecular bone score (TBS, L2–4). We also reviewed the duration of teriparatide treatment, previous vertebral fractures, new vertebral fractures after teriparatide treatment, as well as increases in the P1NP and TRACP-5b levels, total hip and femoral neck BMD, lumbar spine (L2–4) BMD, and TBS.

We evaluated all reported adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE), ver. 5.0-JCOG.[11] We then assessed the potential for a causal relationship between an identified adverse clinical event and the use of a drug according to the Naranjo Adverse Drug Reaction Probability Scale (i.e., Naranjo Probability Scale).[12] Whenever possible, doctors queried patients who stopped using teriparatide injections before 24 months about the reason(s) for drop out. According to the patient chart, we evaluated the relationship between the cited reason(s) and any adverse events.

We also evaluated medication persistence and adherence. We regarded the patient with good adherence who consulted the doctor regularly and continued to be prescribed teriparatide 20 μg once daily via subcutaneous injection (Teriparatide Kit) 24 times without major trouble. The administration period is 24 months including rest period.

Statistical Analyses Statistical tests were performed for generally exploratory purposes. For all tests, $p < 0.05$ was considered statistically significant. The Mann–Whitney U test and Pearson's chi-squared test were used to compare the two groups using Statcel 3 software(OMS Publishing Inc., Saitama, Japan). Kaplan–Meier survival analysis was used to estimate the persistence rates in the two groups using EZR[13], and the comparison of the two groups were analyzed using the log-rank test.

RESULTS

Patient Characteristics We included 158 patients who had received at least one prescription for once-daily teriparatide 20 μg via subcutaneous injection during the study period and who continued treatment for at least 24 months after treatment initiation. Approximately two-thirds (67.1%) of the patients were aged ≥80 years, and accordingly, 52 and 106 patients were classified into Groups A and B, respectively. Both groups were comprised mostly of females (96.2% and 93.4% female in Groups A and B, respectively; Table 1).

The mean height, weight, and eGFR of Group B were significantly inferior to those of Group A (respectively, $p<0.001$, $p=0.006$, $p<0.001$). There were no differences in the frequency of RA or concomitant use of corticosteroids between the groups. Moreover, both groups had a high rate of previous vertebral fracture (77% for Group A, 83% for Group B).

Medication Persistence and Adherence Of the 158 included patients, 74 (46.8%) completed the full course of treatment (24 months). Group A had a significantly higher completion rate than Group B (59.6% *vs*. 40.6%, $p=0.036$) (Table 1). Log-rank test also shows patients in Group B exhibits a greater tendency to drop out than patients in Group A ($p=0.0238$). The patients in Group B tended to continue to drop out from the beginning (Fig. 1).

Reason(s) for Treatment Drop Out The remaining 84 (53.2%) patients dropped out of therapy despite receiving a careful explanation about self-injection. We were able to obtain the reasons for drop out from 47 (56.0%) patients and classified these as personal circumstances, adverse events, and others (Table 2).

Adverse events were the most frequently cited reasons for drop out (70.2%). Patients in Group A were more likely to experience dizziness, vertigo, and a floating sensation, while those in Group B were more likely to experience a decrease in their eGFR, vomiting and nausea, and rash.

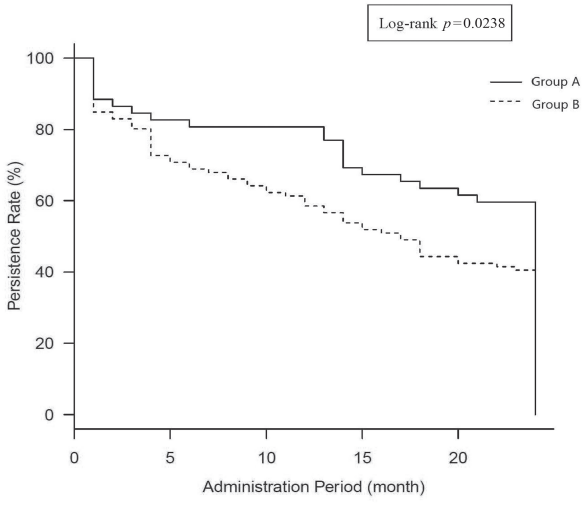

Fig. 1. Persistence Rates of Group A and B

Group A: <80 years old, Group B: ≥80 years old. Patients in Group B exhibited a greater tendency to drop out.

Table 1. Characteristics of Patients with Osteoporosis at the Time of First Teriparatide Prescription

Variables	Group A, 60–79 years	Group B, ≥80 years	*p*-value
Sex (male)	52 (2)	106 (7)	
Age (years), mean ± SD	75.4 ± 3.0	84.2 ± 3.2	
Successful treatment completion, n (%)	31 (59.6%) (N=52)	43 (40.6%) (N=106)	0.036
Drop out, n(%)	21 (40.4%) (N=52)	63 (59.4%) (N=106)	
Drop out at the first injection, n (%)	6 (11.5%) (N=52)	16 (15.1%) (N=106)	
Height (cm), mean ± SD	150.0 ± 6.8 (N=51)	146.2 ± 5.9 (N=96)	<0.001
Weight (kg), mean ± SD	49.4 ± 8.0 (N=51)	46.2 ± 8.8 (N=96)	0.006
BMI (kg/m^2), mean ± SD	21.9 ± 3.3 (N=51)	21.6 ± 3.6 (N=96)	0.281
eGFR (mL/min/1.73^2), mean ± SD	79.2 ± 17.4 (N=49)	67.0 ± 19.4 (N=104)	<0.001
Concomitant rheumatoid arthritis, n (%)	9 (17%) (N=52)	24 (23%) (N=106)	0.438
Concomitant corticosteroid use, n (%)	1 (2%) (N=52)	7 (7%) (N=106)	0.207
Previous fracture, n(%)	40 (77%) (N=52)	88 (83%) (N=106)	0.359
P1NP level (μg/L), mean ± SD	45.2 ± 30.7 (N=51)	49.6 ± 34.1 (N=104)	0.389
TRACP-5b level (mU/dL), mean ± SD	420.3 ± 212.5 (N=51)	465.8 ± 234.2 (N=104)	0.248
Total hip BMD† (g/cm^2), mean ± SD	0.633 ± 0.114 (N=19)	0.590 ± 0.103 (N=41)	0.187
Femoral neck BMD† (g/cm^2), mean ± SD	0.524 ± 0.114 (N=19)	0.492 ± 0.089 (N=41)	0.298
Lumbar spine (L2–4) BMD† (g/cm^2), mean ± SD	0.713 ± 0.116 (N=18)	0.751 ± 0.156 (N=39)	0.514
Lumbar spine (L2–4) TBS‡, mean ± SD	1.217 ± 0.089 (N=18)	1.245 ± 0.083 (N=39)	0.183

BMD† was assessed using dual energy X-ray absorptiometry (DXA) (Horizon-C, USA) scans. We analyzed the extent to which abaloparatide-SC improved skeletal microarchitecture (TBS iNsight software, Switzerland) indirectly using the TBS‡.
SD, standard deviations; BMD, bone mineral density; BMI, body mass index; eGFR, estimated glomerular filtration rate; P1NP, procollagen N-terminal propeptide; TRACP-5b, tartrate-resistant acid phosphatase-5b; TBS, trabecular bone score

Table 2. Reason for Patient Drop Out

Reason	Group A	Group B	Total
Total number of patients who dropped out	14	33	47†
Personal circumstances	2 (14.3%)	8 (24.2%)	10 (21.3%)
"I cannot inject this by myself"		5 (15.2%)	5 (10.6%)
"It is easy to forget this/I do not want to take this"		3 (9.1%)	3 (6.4%)
"I feel stress"	2 (14.3%)		2 (4.3%)
Adverse event	14 (100%)	26 (78.8%)	40 (85.1%)
eGFR decrease		2 (6.1%)	2 (4.3%)
Vomiting/nausea	2 (14.3%)	10 (30.3%)	12 (25.5%)
Rash		3 (9.1%)	3 (6.4%)
Headache	1 (7.1%)	3 (9.1%)	4 (8.5%)
Dizziness/vertigo/floating sensation	4 (28.6%)	1 (3.0%)	5 (10.6%)
Appetite decrease	1 (7.1%)		2 (4.3%)
Blood pressure elevated	1 (7.1%)		1 (2.1%)
Solar sensitivity	1 (7.1%)		1 (2.1%)
Chills		1 (3.0%)	1 (2.1%)
TRACP-5b, elevated		1 (3.0%)	1 (2.1%)
Arrhythmia, tachycardia	1 (7.1%)	1 (3.0%)	2 (4.3%)
Hypercalcemia	1 (7.1%)		1 (2.1%)
Sore throat	1 (7.1%)		1 (2.1%)
Ringing in the ears, increased		1 (3.0%)	1 (2.1%)
Numbness in limb(s)		1 (3.0%)	1 (2.1%)
Alopecia areata, increased	1 (7.1%)		1 (2.1%)
Stomach discomfort		1 (3.0%)	1 (2.1%)
Others	2 (14.3%)	5 (15.2%)	7 (14.9%)
Hospital/nursing home stay	2 (14.3%)	4 (12.1%)	6 (12.8%)
Received other osteoporosis treatment at another clinic		1 (3.0%)	1 (2.1%)

Data are presented as numbers (%).
†The reason for dropout could be determined for 47 of 84 patients (overlapping reasons: n=57).
eGFR, estimated glomerular filtration rate; TRACP-5b, tartrate-resistant acid phosphatase-5b

Adverse Events All adverse events were classified as Grade 1 according to the CTCAE ver. 5.0 and involved only asymptomatic or mild symptoms and/or clinical or diagnostic observations for cases in which intervention was not indicated. The highest Naranjo Probability Scale score regarding a potential causal relationship between an identified untoward clinical event and the drug was +6 (Probable) for a decrease in the eGFR, whereas most other events received scores ranging from -1 (Doubtful) to +4 (Possible; Table 3).

Occurrence of New Vertebral Fractures The previous fracture rates were 74.2% (23/31) in Group A and 86.0% (37/43) in Group B. After treatment, only one new vertebral fracture occurred in a patient in Group B (1/43, 2.3%). Overall, only one of 74 patients (1.35%) who completed the 24-month treatment course developed a new vertebral fracture.

Rates of Change in the BMD, TBS, and Bone Metabolic Marker Levels An investigation of the changes in total hip and femoral neck BMD, lumbar spine (L2–4) BMD, and TBS revealed higher rates in Group B than in Group A; however, these differences were not significant (Table 4).

Although Group B exhibited relatively greater increases in the P1NP and TRACP-5b levels than Group A, these differences were not significant.

Table 3. Adverse Events Evaluated with CTCAE Ver 5.0 -JCOG and the Naranjo Probability Scale

Naranjo Probability Scale†		Adverse event	CTCAE ver 5.0
Totalscore	Interpretation of scores		
+6	Probable.	eGFR decrease	1
+6	Probable.	eGFR decrease	1
+4	Possible.	Vomiting/nausea	1
+4	Possible.	Rash	1
+4	Possible.	Sore throat	1
+4	Possible.	Rash	1
+4	Possible.	Vomiting/nausea	1
+4	Possible.	Arrhythmia	1
+4	Possible.	Stomach discomfort	1
+4	Possible.	Vomiting/nausea	1
+3	Possible.	Vomiting/nausea	1
+3	Possible.	Headache	1
+3	Possible.	Dizziness, vertigo	1
+3	Possible.	Alopecia areata, increased	1
+3	Possible.	Headache	1
+3	Possible.	Appetite decrease	1
+3	Possible.	floating sensation	1
+3	Possible.	Vomiting/nausea	1
+3	Possible.	Chills	1
+3	Possible.	Vomiting/nausea	1
+3	Possible.	Vomiting/nausea	1
+3	Possible.	floating sensation	1
+3	Possible.	Headache	1
+3	Possible.	Rash	1
+3	Possible.	Vomiting/nausea	1
+3	Possible.	Headache	1
+2	Possible.	Blood pressure elevated	1
+2	Possible.	Ringing in the ears, increased	1
+2	Possible.	Vomiting/nausea	1
+2	Possible.	Tachycardia	1
+2	Possible.	floating sensation	1
+1	Possible.	Solar sensitivity	1
0	Doubtful.	Dizziness, vertigo, floating sensation	1
0	Doubtful.	Appetite decrease	1
-1	Doubtful.	Hypercalcemia	1
-1	Doubtful.	Vomiting/nausea	1
-1	Doubtful.	Vomiting/nausea	1
-1	Doubtful.	TRACP-5b level elevated	1
-1	Doubtful.	Vomiting/nausea	1
-2	Doubtful.	Numbness in limb	1
		number of patients	40

Modified from: Naranjo CA *et al*. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239245.
CTCAE, Common Terminology Criteria for Adverse Events; eGFR, estimated glomerular filtration rate; TRACP-5b, tartrate-resistant acid phosphatase-5b;

Table 4. Changes in BMD, TBS, P1NP, and TRACP-5b

	Group A	Group B	*p*-value
Increased rate of total hip BMD	-0.57% (n=12)	1.85% (n=17)	0.232
Increased rate of femoral neck BMD	-0.71% (n=12)	1.55% (n=17)	0.658
Increased rate of lumbar spine (L2–4) BMD	5.54% (n=11)	9.21% (n=15)	0.243
Increased rate of lumbar spine (L2–4) TBS	1.95% (n=11)	3.08% (n=16)	0.217
Increased level of P1NP	149.5% (n=30)	167.8% (n=45)	0.234
Increased level of TRACP-5b	50.3% (n=30)	54.0% (n=45)	0.509

BMD, bone mineral density; P1NP, procollagen N-terminal propeptide; TRACP-5b, tartrate-resistant acid phosphatase-5b; TBS, trabecular bone score

DISCUSSION

In this study of osteoporosis patients who were prescribed teriparatide at a single Japanese orthopedic clinic, 74 (46.8%) of the 158 included patients completed the full course of treatment (24 months). This rate was higher than that described previously (39.1%).[10] Besides, we observed a significantly higher treatment completion rate among younger (<80 years) patients relative to older (≥80 years) patients. This observation did not align with that in a previous report by Niimi *et al*.; that is, they did not observe a significant difference in the rate of treatment completion between older and younger patients.[14] Our results further contradict those of Niimi *et al*. in regard to the reasons provided for teriparatide treatment discontinuation in the older group. Niimi *et al*. reported a high death rate and a high relocation rate to reside with family or at an institution for the aged as the two main reasons for treatment discontinuation. In contrast, we observed that 63 patients in the older group (59.4%, n=106) dropped out, with 16 patients (15.1%) dropping out while using the first Teriparatide Kit. Five of 16 patients had never visited the clinic again. In other words, our findings reflect the difficulty experienced by old-old patients with respect to regular subcutaneous self-injection. Moreover, some of the subjects in our study provided reasons for discontinuation such as "I cannot inject this by myself." and "I don't want to take this." Although adverse events were the most frequently cited reason for drop out in our study (85.1%), a further analysis of the potential causal relationships with these adverse events yielded low Naranjo Probability Scale scores. Lindsay *et al*. also reported that patients who were unwilling to restart osteoporosis treatment were more likely to have discontinued therapy because of adverse events and concerns about safety.[15] Therefore, we assume that most drop outs in our study can be attributed to emotional resistance against medication use. In fact, the patients could convey their honest feelings because they have good relationship with the doctors in the clinic. Therefore, this study may reflect the actual situation of the old-old patients with osteoporosis than the studies in the core hospitals.

Furthermore, we observed a new post-treatment fracture rate of only 1.35%, which was considerably lower than a previously reported rate of 3.7% in a relatively younger population (average age=69.2±6.3).[16] Our results were comparable to those of a large study by Kendler *et al*., in which the 24-month incidence of new radiographic vertebral fractures was 5.4% (28/516) among patients treated with teriparatide and 12.0% (64/533) among those treated with risedronate.[17] As noted previously, few reports have discussed teriparatide use for the treatment of osteoporosis in patients older than 80 years. In a 2014 review, Rizzoli *et al*. investigated the efficacy and safety of alendronate, risedronate, zoledronic acid, clodronate, raloxifene, strontium ranelate, denosumab, teriparatide, and ibandronate.[18] The authors noted the scarcity of efficacy and safety information for oldest old patients (≥80 years), considering the general lack of inclusion of this population in randomized controlled trials (RCTs). However, they also reported a gradual change in this trend, such as an increasing number of subgroup analyses being performed for old-old patients.[18]

In a 2006 study, Boonen *et al*. reported that age did not affect the safety and efficacy of teriparatide in a study of the significant interactions between treatment (teriparatide *vs*. placebo) and age (<75, N=841 *vs*. ≥75 years, N=244) in post-

menopausal women with osteoporosis.[19] Notably, Boonen *et al*. also did not observe any significant differences in the levels of bone turnover markers, femoral neck BMD, vertebral fractures, nonvertebral fragility fractures, height loss, hyperuricemia, or hypercalcemia between the age groups. As mentioned before, Niimi *et al*. observed that teriparatide was useful for the treatment of osteoporosis in older patients and that this usefulness was not affected by age.[14] Likely, this outcome was more related to the increased fracture risk and its association with age. Vandenbroucke *et al*. also investigated the pharmacological management of osteoporosis in the oldest old patients (≥80 years) and observed that, compared to younger patients, older patients experienced a larger absolute risk reduction with treatment due to their higher baseline fracture risk.[20] In other words, it seems that older patients would benefit more significantly from osteoporosis treatment than younger patients.

Finally, we investigated increases in the levels of P1NP, TRACP-5b, total hip and femoral neck BMD, and lumbar spine (L2–4) BMD and TBS. Although all rates tended to be higher in the older group than in the younger group, none of these differences were significant. Niimi *et al*. also reported higher rates of lumbar spine BMD (14.6% *vs.* 12.2%) and femoral neck BMD (4.5% *vs*. 2.9%) in the older subgroup *vs*. the younger subgroup.[14] This finding was consistent with our observations because neither of these differences were significant at 24 months in our study. We also observed a trend of 1.6-fold higher rate of increase in the lumbar spine (L2–4) TBS, a measure of bone quality, in the older group (3.08%) *vs.* the younger group (1.95%). As suggested by Krohn *et al*., a significant increase in the TBS may indicate an improvement in the trabecular structure.[21]

Our study is the first study to focus on the efficacy (e.g., bone quality and safety) of teriparatide and associated treatment adherence in patients with osteoporosis aged ≥80 years. As noted, we reported a lower rate of new vertebral fractures than those observed in previous clinical trials and determined the safety of teriparatide through an analysis of adverse events. Nevertheless, patients in our study were reluctant to perform self-injection and tended to drop out when faced with this prospect. Therefore, we have identified the completion of teriparatide treatment as a serious problem requiring intervention, particularly to the initiation of self-injection.

In the clinic, the doctors kept talking with the patients until they show willingness to agree to the Teriparatide therapy. The nurses provide the first self-injection guidance to the patients with using the genuine injections. Additionally, patients were informed about "a patient-support program".[22] According to the program, the pharmacists encouraged patients to continue teriparatide treatments. Our team medical care might have caused high completion rate.

Our study had some limitations. First, we used claims data obtained from medical records collected at a special community orthopedic clinic. Accordingly, our subject population was small. Second, our subjects may have been considered high-risk, considering the high rates of previous fracture in both groups.

Despite these limitations, we conclude that our results emphasize the importance of successful osteoporosis treatment in super-aging societies. In future work, we hope to share our results and collaborate with fellow clinicians and colleagues in the field of osteoporosis treatment.

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Conflict of interest The authors declare no conflict of interest.

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