Tohoku J. Exp. Med., 2023, **260**, 119-126

Comparison of the Continuation Rate of Twice-Weekly and Weekly Teriparatide Administration in a Rural Area

Hiroyuki Tsuchie,[1] Hidekazu Abe,[2] Norimitsu Masutani[2] and Naohisa Miyakoshi[1]

[1]Department of Orthopedic Surgery, Akita University Graduate School of Medicine, Akita, Akita, Japan
[2]Department of Orthopedic Surgery, Ugo Municipal Hospital, Ogachi-gun, Akita, Japan

Teriparatide plays an important role in the treatment of patients with severe osteoporosis; however, it is meaningless if patients cannot continue. In recent years, the use of a twice-weekly auto-injector teriparatide preparation has become possible. However, its continuation rate and the factors affecting it have not been adequately investigated. Therefore, this study aimed to examine the continuation rate of twice-weekly teriparatide and the factors affecting it. This retrospective study included 143 patients who were administered teriparatide weekly (65 patients) or twice-weekly (78 patients) in a rural hospital. Patient information, such as age, the distance between the hospital and home, family structure, past osteoporosis treatment and fracture, adverse events, and period of teriparatide continuation, were collected. We compared the differences in continuation rates between the twice-weekly and the weekly groups using the Kaplan-Meier curves, and we examined factors influencing teriparatide discontinuation using multivariate analyses. The 12- and 24-month continuation rates of twice-weekly administration of teriparatide were 79.5% and 61%, respectively. The twice-weekly group showed a significantly higher continuation rate ($P < 0.0001$). The multivariate analyses showed that older age and adverse events were identified as risk factors negatively influencing teriparatide continuation ($P = 0.0237$ and $P < 0.0001$, respectively). On the other hand, twice-weekly teriparatide was shown to reduce the risk of discontinuation ($P = 0.0043$). The twice-weekly teriparatide has a considerably higher continuation rate than the weekly teriparatide. Weekly preparation, older age, and adverse event were identified as risk factors negatively influencing teriparatide continuation.

Keywords: continuation rate; discontinuation; teriparatide; twice-weekly; weekly
Tohoku J. Exp. Med., 2023 June, **260** (2), 119-126.
doi: 10.1620/tjem.2023.J022

Introduction

Osteoporosis is characterized by a low bone mass and microarchitectural deterioration of the bone structure, resulting in bone fragility. Patients with osteoporosis are prone to fractures, and this leads to lower-limb muscle weakness and dementia, and causes a decline in activities of daily living. In addition, approximately 30% of all postmenopausal women have osteoporosis (Melton et al. 1992), and there are approximately 13 million patients in Japan (Japanese 2015 Guidelines for Prevention and Treatment of Osteoporosis: http://www.josteo.com/ja/guideline/doc/15_1.pdf). Therefore, osteoporosis is considered a serious public health concern.

Teriparatide [human parathyroid hormone (1-34)] is one of the medicines to treat osteoporosis that has demonstrated potent anabolic effects on bone in several animal models and humans (Andreassen et al. 1999; Peichl et al. 2011), and it plays an important role for patients with severe osteoporosis. However, no matter how strong the therapeutic agent for osteoporosis is, it is meaningless unless the patient continues to use it. There are two types of teriparatide preparations, daily and weekly, with different methods of administration. Daily teriparatide is a genetically modified product and requires daily self-injection, whereas weekly teriparatide is in the form of teriparatide acetate and needs to be injected in the hospital once a week. There have been various reports of studies on continuation rates for daily teriparatide (Arden et al. 2006; Adachi et al. 2007; Ziller et al. 2010; Foster et al. 2011; Kyvernitakis et

Received January 26, 2023; revised and accepted March 7, 2023; J-STAGE Advance online publication March 16, 2023
Correspondence: Hiroyuki Tsuchie, M.D., Department of Orthopedic Surgery, Akita University Graduate School of Medicine, 1-1-1 Hondo, Akita, Akita 010-8543, Japan.
e-mail: tuchikiti@yahoo.co.jp
©2023 Tohoku University Medical Press. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (CC-BY-NC-ND 4.0). Anyone may download, reuse, copy, reprint, or distribute the article without modifications or adaptations for non-profit purposes if they cite the original authors and source properly.
https://creativecommons.org/licenses/by-nc-nd/4.0/

al. 2014; Rajzbaum et al. 2014; Usui et al. 2018; Oishi et al. 2018), however, there are only a few reports on the continuation rate for weekly teriparatide (Oishi et al. 2018; Usui et al. 2018; Mochizuki et al. 2023). Therefore, in our previous study, we examined the continuation rate of weekly teriparatide and the factors that influence the continuation rate (Tsuchie et al. 2020). However, in recent years, it has become possible to use a self-injection preparation twice-weekly with the same teriparatide acetate as the weekly preparation. Furthermore, since the twice-weekly formulation is an auto-injector product, it is not necessary to change the needle each time as in the daily formulation, and it is easy to use. This twice-weekly auto-injector teriparatide preparation has been available in Japan for about three years. However, its continuation rate and the factors affecting it have not been adequately investigated.

This study aimed to examine the continuation rate of twice-weekly teriparatide preparation, the factors affecting it, and to evaluate the difference in the continuation rate from that of weekly teriparatide preparation.

Materials and Methods

Subjects

This study retrospectively reviewed the medical records of 155 Japanese patients administered with teriparatide acetate weekly or twice-weekly at Ugo Municipal Hospital located in a rural northeastern area of Japan between September 2012 and February 2022. The patients were administered with subcutaneous injection of 56.5-μg teriparatide in the hospital once a week or 28.2-μg subcutaneous self-injection with an auto-injector at home twice weekly (Teribone®, Asahi Kasei Pharma Co., Ltd., Tokyo, Japan). We included patients with osteoporosis with a bone mineral density (BMD) of the lumbar spine or femoral neck lower than −2.5 standard deviation (SD) of the T-score or patients with histories of fragile-bone fractures. Patients with a history of metabolic bone disease other than osteoporosis or malignancy were excluded from the present study. Among the cases in which teriparatide was used to promote bone fusion, cases in which teriparatide was discontinued at the discretion of the attending physician after obtaining bone fusion were also excluded. Patients who lived in elderly care facilities were also excluded from this study because the living environment affected the continuation rate. We also excluded patients who switched from weekly administration to twice-weekly administration before completion. Finally, 143 consecutive patients, with a mean age of 78.0 years (59 to 96), were included in this study, 65 of whom used weekly administration (weekly group) and 78 used twice-weekly administration (twice-weekly group).

Patient information included age, sex, the distance by road between the hospital and home, family structure, place of introduction of teriparatide (outpatient or hospitalization), reason for the start of teriparatide administration (fracture or examination of osteoporosis), history of osteoporosis treatment, history of fracture, the presence of rheumatoid arthritis, BMD of the lumbar spine and femoral neck before and after teriparatide administration, adverse events leading to the discontinuation of teriparatide, period of teriparatide continuation, and occurrence of fragility fractures during teriparatide use. We performed BMD measurement within 2 months of starting teriparatide in all patients and measured anteroposterior (AP) views of the lumbar spine from L2 to L4 and the femoral neck. The administration period of weekly teriparatide was up to 18 months until June 2017 and up to 24 months thereafter because the period of insurance coverage in Japan for weekly teriparatide was extended. Patients who had reached the maximum period when teriparatide ended were considered to have completed the treatment. We compared the differences in patient background and continuation rates between the weekly and twice-weekly groups. Furthermore, we examined factors influencing teriparatide discontinuation and adverse events in all patients. In the absence of any events, the date of the last follow-up was considered the endpoint.

Ethical statement

Our study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 1983. This study was approved by the Institutional Review Board for Clinical Research at Ugo Municipal Hospital (approval number: 0302), and informed consent was obtained from all patients enrolled in the study.

Statistical analysis

All continuous variables are expressed as means ± SD. The student's *t*-test, Welch's *t*-test, and Chi-squared (χ^2) test were used to compare the characteristics between the groups. Teriparatide continuation curves were drawn using the Kaplan-Meier method, and the difference between the two groups was analyzed using the generalized Wilcoxon test. A Cox proportional hazards model was used to identify factors associated with the discontinuation of teriparatide. Multivariate logistic regression analysis was used to identify the risk factors associated with the adverse events. Statistical significance was set at $P < 0.05$.

Results

Patient demographic and clinicopathological information are shown in Table 1. The distance by road between the hospital and home in all patients was 9.2 ± 7.6 km (0.2 to 34.3). The number of family members living together was 2.5 ± 1.5 (0 to 9) in all patients. Sixty-nine patients started teriparatide after the following fractures: vertebral body in 51 patients, the femur in 11, pelvis in six, and humerus in one. Fifty-four patients started teriparatide during hospitalization, 43 of whom had fractures. Osteoporosis treatment was prescribed for 59 patients before starting the treatment with teriparatide. Alendronate (Fosamac®; MSD, Tokyo, Japan) was prescribed for 13 patients at 35 mg/

Table 1. Comparison of clinical information between the twice-weekly and weekly groups.

	Twice-weekly	Weekly	*P*
Number	78	65	-
Age	76.9 ± 7.3	79.3 ± 7.9	0.0556
Sex - Male/Female	1/77	6/59	0.0712
Distance between hospital and home (km)	9.9 ± 7.6	8.4 ± 7.5	0.2675
Number of family members living together	1.9 ± 1.1	2.8 ± 1.7	0.0041
Place of introduction of teriparatide - Outpatient/Hospitalization	63/15	26/39	< 0.0001
Reason for the start of teriparatide administration - Fracture/Examination	25/53	44/21	< 0.0001
Past osteoporosis treatment - Present/None	40/38	19/46	0.0125
Past fractures - Present/None	30/48	28/37	0.6975
Rheumatoid arthritis - Present/None	4/74	4/61	0.9206
BMD (g/cm^2) of lumbar spine			
Before starting teriparatide	0.686 ± 0.176	0.679 ± 0.142	0.8320
One year after starting teriparatide	0.662 ± 0.160	0.682 ± 0.144	0.7024
Two years after starting teriparatide	0.785 ± 0.176	0.728 ± 0.273	0.4647
BMD of proximal femur (g/cm^2)			
Before starting teriparatide	0.487 ± 0.112	0.488 ± 0.118	0.9576
One year after starting teriparatide	0.494 ± 0.105	0.486 ± 0.115	0.8484
Two years after starting teriparatide	0.527 ± 0.105	0.449 ± 0.118	0.0829
Adverse event leading to discontinuation of teriparatide - Present/None	8/70	10/55	0.5045
Teriparatide - Completed/Discontinued/Ongoing	36/23/19	22/43/0	-
Duration of teriparatide (months)	17.8 ± 7.9	9.1 ± 8.7	< 0.0001
Occurrence of fragility fractures during teriparatide use - Present/None	1/77	0/65	0.9270

Values are expressed as the number of patients or mean ± SD.
BMD, bone mineral density.

week, risedronate (Actonel®; Eisai, Tokyo, Japan, or Benet®; Takeda Pharmaceutical, Tokyo, Japan) was prescribed for 13 patients at 17.5 mg/week, minodronate (Recarbon®; Ono Pharmaceutical, Osaka, Japan) was prescribed for four patients at 50 mg/4 weeks, ibandronate (Bonviva®, Taisho Toyama Pharmaceutical, Tokyo, Japan) was prescribed for three patients at 1 mg/4 weeks, zoledronic acid (Reclast®, Asahi Kasei Pharma Co., Ltd.) was prescribed for two patients at 5 mg/year, eldecalcitol (Edirol®; Chugai Pharmaceutical, Tokyo, Japan) was prescribed for 20 patients at 0.75 μg/day, bazedoxifene (Viviant®; Pfizer Japan Inc., Tokyo, Japan) was prescribed for eight patients at 20 mg/day, denosumab (Pralia®, Daiichi Sankyo, Tokyo, Japan) was prescribed for two patients at 60 mg/6 months, romosozumab (Evenity®, Amgen K.K., Tokyo, Japan) was prescribed for four patients at 210 mg/month, and elcatonin (Elcitonin®; Asahi Kasei Pharma, Ltd.) was prescribed for one patient at 20 μg/week. Eleven of 60 patients took eldecalcitol and a combination of other osteoporosis drugs (alendronate, risedronate, ibandronate, and bazedoxifene). Excluding the present fracture that triggered the introduction of teriparatide, 58 patients had histories of previous fractures as follows: vertebral body in 25 patients, the femur in 12, distal radius in 12, pelvis in three, proximal tibia in three, ulna in two, sternum in one, distal fibula in one, and metatarsus in one. Two of the 59 patients had a history of two fractures. Teriparatide treatment was completed in 58 of 124 patients (46.8%), excluding 19 patients receiving ongoing treatment. Thirty-six of the 59 patients (61%) have completed teriparatide treatment in the twice-weekly group, and 22 of 65 patients (33.8%) have completed teriparatide treatment in the weekly group. In the twice-weekly group, the 6-month continuation rate was 87.2% (68 continuations and 10 discontinuations), the 12-month continuation rate was 79.5% (62 continuations and 16 discontinuations), and the 18-month continuation rate was 70.8% (51 continuations and 21 discontinuations). The duration of teriparatide in all patients was 13.9 ± 9.3 months (0 to 24). Only one patient in the twice-weekly group had a fragility fracture of the thoracic spine during treatment with teriparatide.

Teriparatide discontinuation was confirmed in 66 cases, of which 23 were in the twice-weekly group, and 43 were in the weekly group. In all patients, 18 cases (27.3%) were discontinued due to adverse events, which was the most common reason for discontinuation. Nausea was the most common adverse event in seven cases, followed by malaise and body pain in three cases each, dizziness and hypertension in two cases each, and itching in one case. In the twice-weekly group, adverse events accounted for 34.8%, which was the most common reason for discontinuation (Table 2). Meanwhile, difficulty in continuing to go to the hospital was the most common reason for discontinuation at 37.2% in the weekly group.

Table 2. Reasons for the discontinuation of teriparatide administration.

	Twice-weekly (%)	Weekly (%)
Number of discontinuation patients	23	43
Adverse event	8 (34.8)	10 (23.3)
Nausea	3	4
Dizziness	2	0
Malaise	1	2
Itching	1	0
Body pain	1	2
Hypertension	0	2
Dropout from outpatient treatment	7 (30.4)	7 (16.3)
No hope for osteoporosis treatment	1 (4.3)	3 (7.0)
Financial burden	2 (8.7)	0 (0)
Difficult to continue going to the hospital	0 (0)	16 (37.2)
The hassle of waiting in the hospital after injection	-	1 (2.3)
Difficult to self-inject	1 (4.3)	-
Resistance to self-injection	3 (13.0)	-
Death form other illness	1 (4.3)	1 (2.3)
Unknown	0 (0)	5 (11.6)

Values are expressed as the number of patients (%).

The twice-weekly group had a longer duration of teriparatide ($P < 0.0001$) and a smaller number of people living together ($P = 0.0041$) than the weekly group (Table 1). Furthermore, in the twice-weekly group, there were significantly more patients who started as outpatients ($P < 0.0001$), started treatment for reasons other than fractures ($P < 0.0001$), and had a past osteoporosis treatment ($P = 0.0125$). In the Kaplan-Meier curves on teriparatide continuation between the two groups, the twice-weekly group showed a significantly higher continuation rate ($P < 0.0001$) (Fig. 1).

The uni- and multivariate analysis showed no obvious factors associated with teriparatide discontinuation only in the weekly or the twice-weekly groups (Table 3). However, the uni- and multivariate analyses in all patients showed that older age and adverse events were risk factors negatively influencing teriparatide continuation ($P = 0.0237$ and $P < 0.0001$, respectively) (Table 4). On the other hand, twice-weekly administration was shown to reduce the risk of discontinuation of teriparatide ($P = 0.043$). The univariate analysis showed no obvious factors associated with adverse event in all patients (Table 5).

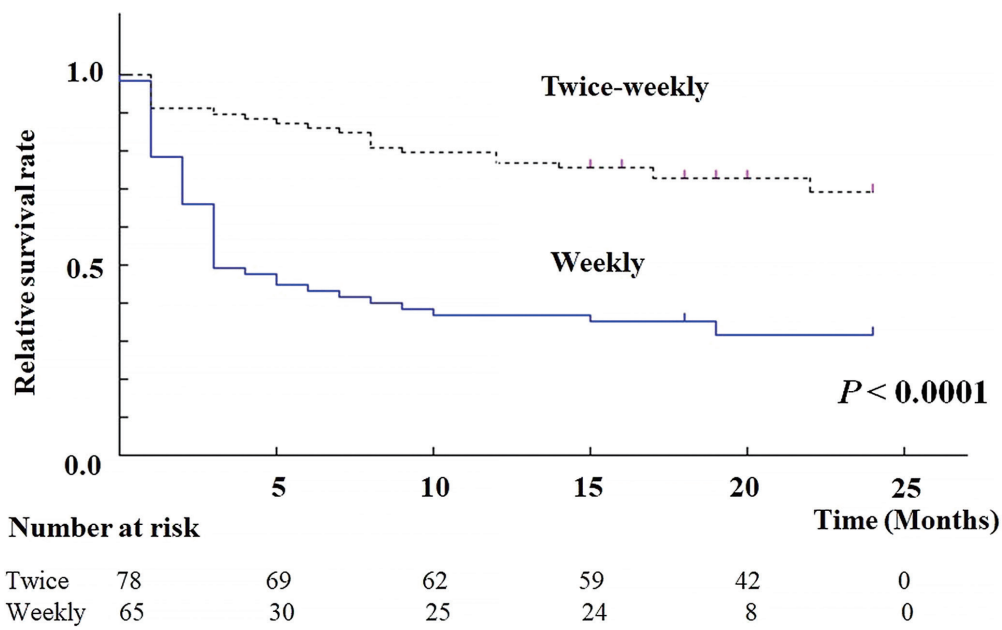

Fig. 1. The Kaplan-Meier curves of teriparatide continuation between the twice-weekly and weekly groups. The curves for the two groups showed significant differences ($P < 0.0001$).

Table 3. Univariate and multivariate analysis of factors affecting the discontinuation of teriparatide in each patient administered with teriparatide weekly or twice weekly.

Variables	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
Twice-weekly						
Age	1.023	0.958-1.068	0.4460			
Distance between hospital and home	1.012	0.958-1.068	0.6748			
Number of family members living together	0.891	0.493-1.610	0.7016			
Starting at hospitalization	0.857	0.291-2.519	0.7789			
Reason for the start of teriparatide - Fracture	1.201	0.509-2.835	0.6765			
Past osteoporosis treatment	1.001	0.445-2.293	0.9796			
Past fractures	1.406	0.616-2.212	0.4187			
BMD of lumbar spine	2.886	0.294-28.339	0.3631			
BMD of proximal femur	0.478	0.012-19.410	0.6958			
Weekly						
Age	1.063	1.014-1.114	0.0115	1.043	0.994-1.093	0.0834
Distance between hospital and home	1.005	0.965-1.047	0.8093			
Number of family members living together	0.986	0.802-1.213	0.8955			
Starting at hospitalization	2.910	1.414-5.990	0.0037	1.909	0.590-6.172	0.0037
Reason for the start of teriparatide - Fracture	2.842	1.283-6.296	0.0101	1.439	0.395-5.239	0.5809
Past osteoporosis treatment	0.808	0.414-1.575	0.5310			
Past fractures	1.047	0.572-1.913	0.8825			
BMD of lumbar spine	0.862	0.071-10.501	0.9070			
BMD of proximal femur	4.814	0.125-185.571	0.3990			

OR, odds ratio; CI, confidence interval; BMD, bone mineral density.

Table 4. Univariate and multivariate analyses of factors affecting the discontinuation of teriparatide in all patients.

Variables	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
Age	1.056	1.018-1.096	0.0037	1.043	1.006-1.082	0.0237
Sex - female	1.093	0.343-3.484	0.8810			
Distance between hospital and home	1.001	0.969-1.035	0.9326			
Number of family members living together	1.071	0.889-1.290	0.4691			
Starting at hospitalization	2.688	1.646-4.390	< 0.0001	1.808	0.796-4.106	0.1568
Reason for the start of teriparatide - Fracture	2.597	1.557-4.331	0.0003	1.090	0.461-2.576	0.8446
Past osteoporosis treatment	0.719	0.435-1.189	0.1988			
Past fractures	1.238	0.761-2.014	0.3891			
Rheumatoid arthritis	1.221	0.443-3.358	0.6989			
BMD of lumbar spine	1.647	0.320-8.480	0.5505			
BMD of proximal femur	1.557	0.121-20.024	0.7338			
Adverse event of teriparatide	4.530	2.605-7.877	< 0.0001	4.186	2.374-7.380	< 0.0001
Twice-weekly	0.301	0.180-0.504	< 0.0001	0.438	0.249-0.772	0.0043

OR, odds ratio; CI, confidence interval; BMD, bone mineral density.

Discussion

Our study shows that the twice-weekly teriparatide preparation has a significantly higher continuation rate than the weekly teriparatide preparation. In addition, the use of the weekly preparation was a significant risk factor for teriparatide discontinuation. The proportion of patients differed between the two groups due to various factors, such as the number of family members living together, place at the start of the administration, the reason for starting administration, and the presence or absence of past osteoporosis treatment. In particular, whether osteoporosis treatment

Table 5. Univariate analyses of factors affecting the adverse event in all patients.

Variables	OR	95% CI	*P*
Age	0.978	0.917-1.042	0.4926
Sex - female	0.857	0.097-7.561	0.8896
Distance between hospital and home	1.008	0.946-1.075	0.8016
Number of family members living together	1.266	0.887-1.806	0.1940
Starting at hospitalization	0.429	0.133-1.377	0.1549
Reason for the start of teriparatide - Fracture	0.492	0.174-1.393	0.1817
Past osteoporosis treatment	2.521	0.915-6.948	0.0739
Past fractures	1.200	0.443-3.250	0.7198
BMD of lumbar spine	0.543	0.023-12.920	0.7060
BMD of proximal femur	13.790	0.110-1,735.532	0.2875
Twice-weekly	0.629	0.233-1.699	0.3602

OR, odds ratio; CI, confidence interval; BMD, bone mineral density.

was initiated by a fracture or an examination may have a significant impact. However, multivariate analysis with these factors showed its usefulness for the continuation rate of the twice-weekly preparation. Among the patients using the weekly preparation in the current study, patients who discontinued due to difficulty going to the hospital were higher than those who discontinued due to adverse events. The distance between the home and the hospital and the number of people living with the family were not risk factors for discontinuation in this study, and similar results were obtained in the previous study targeting only the weekly preparation (Tsuchie et al. 2020). The hospital surveyed in this study is located in a rural area where transportation is very inconvenient, and there is almost no public transportation, such as trains and buses, in the vicinity of the hospital. Therefore, many patients need to go to the hospital by private car, and the difference in distance of several kilometers may not be so problematic. The frequency of hospital visits is expected to be an important factor in the continuation of treatment. In addition, teriparatide is often used in patients with severe osteoporosis and sarcopenia, so the frequency of hospital visits may have a significant impact even in cities. The convenience of the twice-weekly preparation, which does not require frequent visits, may have contributed to the improvement in its continuation rate.

The continuous use of the drug for osteoporosis treatment is important to fully demonstrate its effect. The injection preparation has a higher continuation rate than oral preparation, and the continuation rate of daily teriparatide preparation for 12 months after the start of use ranges from 43.1 to 87% (Arden et al. 2006; Adachi et al. 2007; Cotté et al. 2010; Ziller et al. 2010; Foster et al. 2011; Hadji et al. 2014; Kyvernitakis et al. 2014; Rajzbaum et al. 2014; Oishi et al. 2018; Usui et al. 2018). On the other hand, there are only a few reports on weekly teriparatide preparation. Usui et al. (2018) reported that the continuation rate after 1 year was 23.2% for weekly teriparatide and 43.1% for daily teriparatide. Mochizuki et al. (2023) reported that the continuation rate after 1 year was 66.7% for weekly teriparatide and 80.4% for daily teriparatide, indicating that the continuation rate was relatively high for daily teriparatide. All the reports on the continuation rate of the once-weekly preparation were for 12 months, and there were no longer-term reports. Although the completion rate of weekly formulation at 18 or 24 months was 22.7% in our previous study, the continuation rate of the weekly product in this study was 33.8% (Tsuchie et al. 2020). In the previous study, it is considered that the continuation rate was low because there were patients who were continuing treatment. Regarding the twice-weekly teriparatide preparation, only Fujita et al. (2022) reported a continuation rate of 47.5% after 1 year, but there are no reports showing longer-term continuation rates. In our study, twice-weekly teriparatide preparation had a 1-year continuation rate of 79.5% and a 2-year completion rate of 61%, with a higher continuation rate than the weekly preparation. We were able to show long-term retention rates up to 2 years later. In the report of Fujita et al. (2022), eight cases were still under treatment at 1-year, but in our study, 19 cases were still ongoing at 2-years. Moreover, more than 1 year has passed in all cases. Therefore, it is inferred that the continuation rate at 1-year is more strictly evaluated in our study. Considering the large number of patients who are continuing the treatment, it is expected that the 2-year continuation rate will be even higher.

Another risk factor for discontinuation is old age. Studies have examined factors that affect the continuation rate, and elderly with complications and decreased mobility were mentioned as factors increasing the rate of dropout from treatment (Fahrleitner-Pammer et al. 2017; Oishi et al. 2018). In addition, declining motivation is more likely to occur in elderly people, which may result in a decrease in continuation rates. Some researchers pointed out the importance of a detailed explanation about the fracture-prevention effects of osteoporosis treatment, and each patient's own or patient family's awareness of the need for osteoporosis treatment can affect the continuation rate (McHorney

et al. 2007; Kishimoto and Maehara 2015). It is necessary to cooperate with people of various occupations, such as nurses, doctors, and liaison services to help understand the importance of osteoporosis treatment and improve its continuation rate (Moriwaki and Noto 2017).

Similar to the results of our study, a past report has reported that the occurrence of an adverse event has a significant impact on discontinuation (Fujita et al. 2022). Low BMD in the femur at the time of initiation of teriparatide and self-injection in the morning were also listed as risk factors in the past report. In our study, BMD was not listed as a risk factor for either the femur or the lumbar spine. Because there are still few reports like this study, future studies on a larger number of patients is necessary for a more detailed analysis.

In this study, BMD in the lumbar vertebrae increased with both formulations, with a stronger tendency to increase with the twice-weekly administration of teriparatide. Previous reports comparing weekly and twice-weekly administration have also showed a stronger tendency for bone density to increase with twice-weekly administration (Sugimoto et al. 2019). On the other hand, BMD in the proximal femur tended to decrease with weekly administration in this study. The weak effect of weekly teriparatide administration on the increase of BMD in the proximal femur has been often reported (Ifuku et al. 2019). Although the effect of the twice-weekly administration of teriparatide on the proximal femur is not yet clear, an increase in BMD was observed in this study, in contrast with that observed in the weekly administration of teriparatide. The twice-weekly administration of teriparatide may also be superior in terms of stimulating an increase in bone density.

A limitation of this study was the small number of patients with osteoporosis. Some previous reports using teriparatide included a larger number of cases and some studies on daily teriparatide targeted over 1,000 patients (Arden et al. 2006; Foster et al. 2011). Another limitation is that adverse events cannot be accurately assessed. In the past reports, the incidence of all adverse events in weekly preparation was approximately 90%, and adverse events made it difficult to continue weekly teriparatide in 9.8 to 19.3% (Nakamura et al. 2012; Sugimoto et al. 2019). In the current study, the incidence of adverse events made it difficult to continue weekly teriparatide in 15.4%, which was similar to the results reported in the past. Ideally, the occurrence of all adverse events could be assessed, but mild adverse events were often not documented in medical records; therefore, we only evaluated the strong side effects that make it difficult to continue teriparatide. In addition, it is necessary to investigate the risk factors for the occurrence of adverse events that greatly affect the discontinuation of teriparatide, but no clear factors could be identified in this study. One of the reasons for this was that the evaluation items surveyed in this study have few items that were related to the patient's own body. In future studies, it will be necessary to incorporate information related to the patient's body, such as blood sample data and allergies, and conduct a new evaluation with a larger number of patients. Although there are various limitations, no studies have examined the comparison of the continuation rates between twice-weekly teriparatide and weekly teriparatide, which is important, especially for twice-weekly teriparatide. To the best of our knowledge, this study is the first to investigate the comparison of the continuation rates of twice-weekly teriparatide and weekly teriparatide in a rural area. It is inappropriate to use data from multiple hospitals at different locations to evaluate the distance between the hospital and the patient's home, and it is necessary to consider a single hospital. Although it will take time to increase the number of cases, including sufficient and long-term patient information, further studies need to be conducted in the future.

In conclusion, the twice-weekly teriparatide preparation has a considerably higher continuation rate than the weekly teriparatide preparation. Moreover, old age was a risk factor negatively influencing teriparatide continuation, and it may be important to motivate patients themselves and their families to treat osteoporosis.

Author Contributions

Tsuchie, H., Abe, H., Masutani, N., and Miyakoshi, N. were involved in the planning and revision of this research. Tsuchie, H., Abe, H., and Masutani, N. collected the clinical data. Tsuchie, H. analyzed the raw data. Tsuchie, H. wrote this manuscript. Miyakoshi, N. reviewed this manuscript.

Conflict of Interest

The authors declare no conflict of interest.

References

Adachi, J.D., Hanley, D.A., Lorraine, J.K. & Yu, M. (2007) Assessing compliance, acceptance, and tolerability of teriparatide in patients with osteoporosis who fractured while on antiresorptive treatment or were intolerant to previous antiresorptive treatment: an 18-month, multicenter, open-label, prospective study. *Clin. Ther.*, **29**, 2055-2067.

Andreassen, T.T., Ejersted, C. & Oxlund, H. (1999) Intermittent parathyroid hormone (1-34) treatment increases callus formation and mechanical strength of healing rat fractures. *J. Bone Miner. Res.*, **14**, 960-968.

Arden, N.K., Earl, S., Fisher, D.J., Cooper, C., Carruthers, S. & Goater, M. (2006) Persistence with teriparatide in patients with osteoporosis: the UK experience. *Osteoporos. Int.*, **17**, 1626-1629.

Cotté, F.E., Fardellone, P., Mercier, F., Gaudin, A.F. & Roux, C. (2010) Adherence to monthly and weekly oral bisphosphonates in women with osteoporosis. *Osteoporos. Int.*, **21**, 145-155.

Fahrleitner-Pammer, A., Papaioannou, N., Gielen, E., Feudjo Tepie, M., Toffis, C., Frieling, I., Geusens, P., Makras, P., Boschitsch, E., Callens, J., Anastasilakis, A.D., Niedhart, C., Resch, H., Kalouche-Khalil, L. & Hadji, P. (2017) Factors associated with high 24-month persistence with denosumab: results of a real-world, non-interventional study of women with postmenopausal osteoporosis in Germany, Austria, Greece, and Belgium. *Arch. Osteoporos.*, **12**, 58.

Foster, S.A., Foley, K.A., Meadows, E.S., Johnston, J.A., Wang, S.S., Pohl, G.M. & Long, S.R. (2011) Adherence and persis-

tence with teriparatide among patients with commercial, Medicare, and Medicaid insurance. *Osteoporos. Int.*, **22**, 551-557.

Fujita, R., Endo, T., Takahata, M., Haraya, K., Suzuki, H., Oda, I., Kanayama, M., Asano, T., Shigenobu, K., Iwata, A., Yamada, K., Takeuchi, H., Ohura, H., Yoneoka, D. & Iwasaki, N. (2022) Real-world persistence of twice-weekly teriparatide and factors associated with the discontinuation in patients with osteoporosis. *J. Bone Miner. Metab.*, **40**, 782-789.

Hadji, P., Felsenberg, D., Amling, M., Hofbauer, L.C., Kandenwein, J.A. & Kurth, A. (2014) The non-interventional BonViva Intravenous Versus Alendronate (VIVA) study: real-world adherence and persistence to medication, efficacy, and safety, in patients with postmenopausal osteoporosis. *Osteoporos. Int.*, **25**, 339-347.

Ifuku, E., Yoshimura, T., Uzawa, T. & Hokonohara, T. (2019) Safety and efficacy in actual clinical practice of once-weekly subcutaneous teriparatide for osteoporosis patients with a high fracture risk. *Osteoporos. Sarcopenia*, **5**, 44-50.

Kishimoto, H. & Maehara, M. (2015) Compliance and persistence with daily, weekly, and monthly bisphosphonates for osteoporosis in Japan: analysis of data from the CISA. *Arch. Osteoporos.*, **10**, 231.

Kyvernitakis, I., Kostev, K., Kurth, A., Albert, U.S. & Hadji, P. (2014) Differences in persistency with teriparatide in patients with osteoporosis according to gender and health care provider. *Osteoporos. Int.*, **25**, 2721-2728.

McHorney, C.A., Schousboe, J.T., Cline, R.R. & Weiss, T.W. (2007) The impact of osteoporosis medication beliefs and side-effect experiences on non-adherence to oral bisphosphonates. *Curr. Med. Res. Opin.*, **23**, 3137-3152.

Melton, L.J. 3rd, Chrischilles, E.A., Cooper, C., Lane, A.W. & Riggs, B.L. (1992) Perspective. How many women have osteoporosis? *J. Bone Miner. Res.*, **7**, 1005-1010.

Mochizuki, T., Yano, K., Ikari, K. & Okazaki, K. (2023) Comparison of different parameters between daily and twice-weekly teriparatide in postmenopausal women with severe osteoporosis. *J. Bone Miner. Metab*., **41**, 220-226.

Moriwaki, K. & Noto, S. (2017) Economic evaluation of osteoporosis liaison service for secondary fracture prevention in postmenopausal osteoporosis patients with previous hip fracture in Japan. *Osteoporos. Int.*, **28**, 621-632.

Nakamura, T., Sugimoto, T., Nakano, T., Kishimoto, H., Ito, M., Fukunaga, M., Hagino, H., Sone, T., Yoshikawa, H., Nishizawa, Y., Fujita, T. & Shiraki, M. (2012) Randomized Teriparatide [human parathyroid hormone (PTH) 1-34] Once-Weekly Efficacy Research (TOWER) trial for examining the reduction in new vertebral fractures in subjects with primary osteoporosis and high fracture risk. *J. Clin. Endocrinol. Metab.*, **97**, 3097-3106.

Oishi, T., Fujita, T., Nishida, T., Hagiwara, K., Kurokawa, K., Yamamoto, M., Suzuki, D. & Sugiura, K. (2018) Comparison of continuation rates of osteoporosis treatment injection preparations and examination on factors involved in dropout. *Annual of Enshu Hospital*, **24**, 27-32 (in Japanese).

Peichl, P., Holzer, L.A., Maier, R. & Holzer, G. (2011) Parathyroid hormone 1-84 accelerates fracture-healing in pubic bones of elderly osteoporotic women. *J. Bone Joint Surg. Am.*, **93**, 1583-1587.

Rajzbaum, G., Grados, F., Evans, D., Liu-Leage, S., Petto, H. & Augendre-Ferrante, B. (2014) Treatment persistence and changes in fracture risk, back pain, and quality of life amongst patients treated with teriparatide in routine clinical care in France: results from the European Forsteo Observational Study. *Joint Bone Spine*, **81**, 69-75.

Sugimoto, T., Shiraki, M., Fukunaga, M., Kishimoto, H., Hagino, H., Sone, T., Nakano, T., Ito, M., Yoshikawa, H., Minamida, T., Tsuruya, Y. & Nakamura, T. (2019) Study of twice-weekly injections of Teriparatide by comparing efficacy with once-weekly injections in osteoporosis patients: the TWICE study. *Osteoporos. Int.*, **30**, 2321-2331.

Tsuchie, H., Miyakoshi, N., Kasukawa, Y., Abe, H., Masutani, N. & Shimada, Y. (2020) Factors affecting continuation of weekly teriparatide administration in rural areas. *J. Bone Miner. Metab.*, **38**, 248-253.

Usui, T., Funagoshi, M., Seto, K., Ide, K., Tanaka, S. & Kawakami, K. (2018) Persistence of and switches from teriparatide treatment among women and men with osteoporosis in the real world: a claims database analysis. *Arch. Osteoporos.*, **13**, 54.

Ziller, V., Zimmermann, S.P., Kalder, M., Ziller, M., Seker-Pektas, B., Hellmeyer, L. & Hadji, P. (2010) Adherence and persistence in patients with severe osteoporosis treated with teriparatide. *Curr. Med. Res. Opin.*, **26**, 675-681.