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Effectiveness of Weekly Teriparatide Injection in Postmenopausal Patients with Hip Fractures

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Background: Teriparatide is an effective anabolic agent used in the treatment of severe osteoporosis. In addition, it is also used to promote fracture healing. The purpose of this double-blind randomized controlled trial was to evaluate the influence of weekly teriparatide administration on bone formation in hip fracture patients.

Methods: The control group (n = 41) was composed of patients treated with normal saline other than teriparatide, and the teriparatide group (n = 51) consisted of patients who received weekly teriparatide. Bone turnover markers, C-terminal telopeptide (CTx) and osteocalcin (OC), were assessed through blood tests at the initial hospital visit and 3-month, 6-month, and 1-year follow-ups. Dual-energy X-ray absorptiometry was performed 5 days postoperatively and at 1-year postoperative follow-up. The degree of fracture union was evaluated by comparing the radiographic union scoring system for hips using Radiographic Union Score for Hip (RUSH) scores between the two groups at 3 months, 6 months, and 1 year after surgery.

Results: Evaluation of the rate of change in bone mineral density over 1 year showed that the lumber bone mineral density increased by more than 7% in the experimental group. The control group did not show a difference between the CTx and OC at 6 months, but the difference between the CTx and OC values was large at 6 months in the experimental group. The mean RUSH score was significantly different between the control group and the experimental group: 12.105 and 15.476, respectively ($p = 0.004$), at 3 months and 18.571 and 22.389, respectively, at 6 months ($p = 0.006$).

Conclusions: Weekly use of teriparatide improved fracture healing, bone formation, and clinical outcomes at 1 year after hip fracture surgery by the anabolic window effect.

Keywords: *Teriparatide, Postmenopausal osteoporosis, Hip fractures*

The Organisation for Economic Co-operation and Development (OECD) defines the population over the age of 65 years as an aged population, and the aging of the world's population is accelerating. In particular, South Korea's aging population accounts for 14.3% (2018) of the total population, which ranks 36th among the OECD countries.[1] Postmenopausal women are at an increased risk of osteoporotic fractures as they age. Among the osteoporotic fractures, hip fractures have a poor prognosis with a mortality rate of 10%–20% within 1 year.[2] It is estimated that there will be 4.5 million such fractures worldwide by 2050.[3]

For hip fractures represented by intertrochanteric fractures of the femur, intramedullary (IM) nail fixation is a common treatment.[4] However, some patients have complications related to fracture healing due to delayed union, nonunion, and malunion.[5] To overcome these problems, optimal surgical methods and implant design improvement have been suggested.[6] However, bone metabolism related to osteoporosis also acts as an important factor.[7]

For this reason, the use of parathyroid hormone

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(PTH) agents as osteoporosis drugs that can increase osteoblastic activity after the surgical treatment of fractures is increasing.[8] Studies have reported that PTH or PTH recombinant plays a major role in bone fracture healing.[9,10] However, well-established randomized controlled trials (RCTs) reporting the results of PTH use in hip fracture patients are very rare. In addition, although there are studies that show teriparatide affects bone formation, few studies have evaluated the status of bone union in patients with osteoporotic fractures after weekly teriparatide therapy.[11,12] Therefore, the purpose of this study was to conduct a double-blind RCT to evaluate the influence of weekly teriparatide use on bone formation in hip fracture patients.

METHODS

The study protocol was approved by the Institutional Review Board of Gyeongsang National University Hospital (No. 2018-02-003) and registered with the Clinical Research Information Service (Registration No. KCT0003852). Informed consent was obtained from all patients.

Study Design

Patients with hip fractures were randomly divided. The control group was composed of patients treated with normal saline, and the teriparatide group consisted of patients who received weekly teriparatide for at least 3 months. After receiving informed consent, all were screened to ensure there were no contraindications that would exclude them from receiving teriparatide medication. Hip fractures were defined as femoral neck fractures and intertrochanteric fractures. All fracture patients underwent osteosynthesis surgery with IM nailing (Gamma3-Stryker, PFNA-Depuy Synthes), the femoral neck system (FNS, Depuy Synthes), or multiple pinning (6.5-mm cannulated screw, Tradimedics).

Osteoporosis was defined as a bone mineral density (BMD) T-score of < –2.5 at the lumber spine femoral neck. Patients were excluded if they had evidence of decreased renal function (creatinine clearance < 35.0 mL/min), history of malignancy, hypocalcemia (serum calcium level < 8 mg/dL), significant heart disease, or psychiatric disease. In addition, patients were excluded if they had already taken teriparatide or had PTH-related sensitivity.

Study Participants

Among the patients who visited our hospital from March 2017 to April 2020, 340 female patients aged 65 years or older who underwent surgery for hip fractures were included. A total of 119 patients meeting the exclusion criteria were excluded from the study. Therefore, a total of 221 patients were selected as the participants of this study. Of the 221 patients, 122 patients were treated with teriparatide (teriparatide group), and 99 patients were treated with normal saline other than teriparatide (control group). Among the selected teriparatide and control groups, those who had been treated with teriparatide or normal saline for at least 3 months were considered as the final study participants. As 71 patients in the teriparatide group and 58 patients in the control group did not use the drug for 3 months or more, the final study population included 51 patients in the teriparatide group and 41 patients in the control group (Fig. 1). The teriparatide group patients

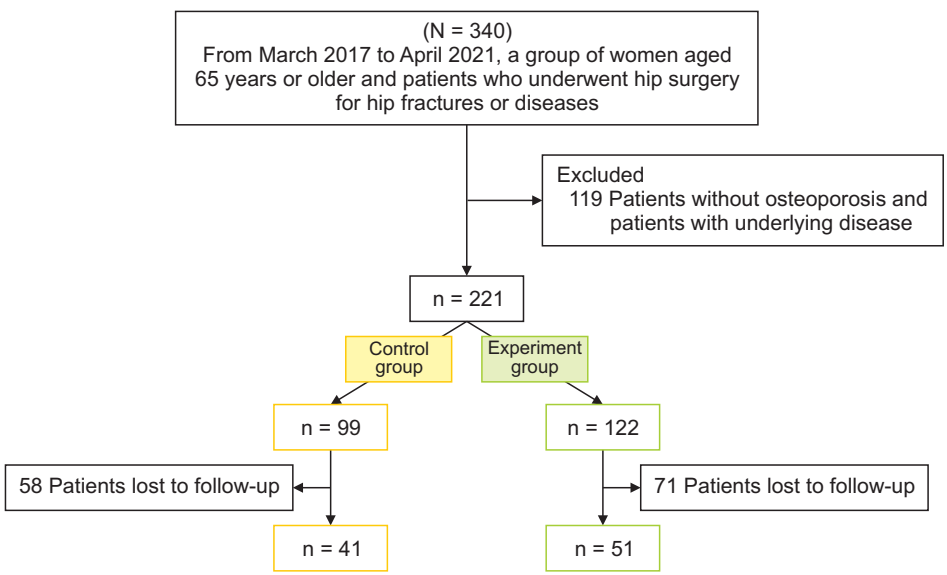

Fig. 1. Flowchart of this study.

were treated with once-weekly injection of teriparatide (56.5 μg/wk) and the control group patients were treated with normal saline during the same period. During the research period, calcium and vitamin D supplements were given to all patients. The number of times the case group received teriparatide was 28.36 ± 16.57 (range, 1–78).

BMD Measurements

Areal BMD of the lumbar spine and femoral neck was measured by dual-energy X-ray absorptiometry (DEXA) using Hologic Dual Energy X-Ray Absorptiometry (Hologic Inc.). All scans were performed on the same densitometer. DEXA was performed 5 days postoperatively and followed up 1 year postoperatively.

Biochemical Measurements

Bone turnover markers, C-terminal telopeptide (CTx) and osteocalcin (OC), were confirmed through blood tests using the Roche Diagnostic Elecsys assay at the initial hospital visit and 3-month, 6-month, and 1-year follow-ups. All measurements were performed in the morning in fasting conditions.

Fracture Union Scoring System

X-ray examination was done postoperatively and at 3-month, 6-month, and 1-year follow-ups. The degree of fracture union was evaluated by comparing the radiographic union scoring system for hips using Radiographic Union Score for Hip (RUSH) scores between the two groups at 3 months, 6 months, and 1 year after surgery.

Clinical Evaluation Criterion

Walking ability and physical function were estimated by evaluating the Koval score of each group. The categories of ambulation were as follows: (1) independent community ambulator; (2) community ambulator with a cane; (3) community ambulator with walker/crutches; (4) independent household ambulator; (5) household ambulator with a cane; (6) household ambulator with walker or crutches; and (7) nonfunctional ambulator.

Statistical Analysis

We used the chi-square or Fisher's exact tests for categorical variables and the independent *t*-test for numerical variables. All two-sided *p*-values of < 0.05 were considered significant. Statistical analyses were conducted using IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Demographic Factors

The average age of the teriparatide group selected for the final study was 76.8 ± 8.32 years, and the average Koval score was 2.86 ± 1.75 points. However, the average age of the control group selected for the final study was 75.0 ± 8.02 years, and the average Koval score was 1.96 ± 1.97 points. Table 1 summarizes the patient demographic profiles.

Study Results

The mean initial CTx level in the control group and teriparatide group was 0.508 ng/mL and 0.498 ng/mL, respectively, the 6-month mean CTx level was 0.315 ng/mL and 0.549 ng/mL, respectively ($p = 0.035$), and the 1-year follow-up mean CTx level was 0.398 ng/mL and 0.401 ng/mL, respectively ($p = 0.979$). At 6 months, the mean CTx level decreased in the control group and slightly recovered at 1 year. In the teriparatide group, CTx slightly increased at 6 months, but it decreased at 1 year (Fig. 2). The initial mean OC level in the control group and the teriparatide group was 16.8 ng/mL and 15.5 ng/mL, respectively ($p = 0.754$), the 6-month mean OC level was 14.8 ng/mL and 30.4 ng/mL, respectively ($p = 0.095$), and the 1-year follow-up mean OC level was 13.5 ng/mL and 29.7 ng/mL, respectively ($p = 0.023$). At the 1-year follow-up, the mean OC level decreased in the control group. However, in the teriparatide group, OC continuously increased until 1 year (Fig. 3).

To evaluate the anabolic window of teriparatide, we compared the difference between the CTx and OC values in the control and teriparatide groups. In the control group, the CTx and OC values were slightly different at 3–6 months, but the values were almost the same at 1 year (Fig. 4A). However, in the teriparatide group, the difference between CTx and OC was large at 6 months, and the difference was larger at 1 year (Fig. 4B).

During the 1-year follow-up period, there were no significant differences in lumber BMD between the teriparatide group and control group (initial $p = 0.158$, 1-year $p = 0.561$). However, 1-year lumber BMD (0.698) of the teriparatide group increased compared to the initial BMD (0.662), while 1-year lumber BMD (0.731) of the control group was almost the same as the initial BMD (0.727). Similarly, there were no significant differences in femoral neck BMD during the 1-year follow-up period between the teriparatide group and control group (initial $p = 0.713$, 1-year $p = 0.146$). However, the 1-year femoral neck BMD (0.499) of the teriparatide group increased compared to

Table 1. Patients' Demographics

Variable	Teriparatide group (n = 51)	Control group (n = 41)	*p*-value
Age (yr)	76.8 ± 8.32	75.0 ± 8.02	0.903
Average ambulatory status (Koval score)	2.86 ± 1.75	1.96 ± 1.97	0.838
Diagnose			0.638
Intertrochanteric fractures	40	31	
Femoral neck fractures	11	10	
Hip injury			0.658
Right	20	19	
Left	25	20	
Both	6	2	
Treatment for the disease			0.374
IM nail fixation	40	31	
Multiple pin fixation	6	5	
Femoral neck system	5	5	
Comorbidity			0.518
Hypertension	21	26	
Diabetes mellitus	9	11	
Dyslipidemia	3	5	
Stroke	8	1	
Heart disease	6	9	
Liver Disease	1	0	
Lung disease	0	7	
Rheumatic arthritis	2	2	
Other	3	3	

IM: intramedullary.

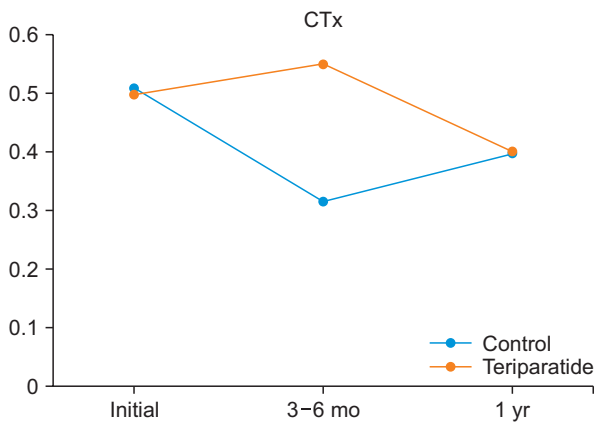

Fig. 2. Change of C-terminal telopeptide (CTx) during 1-year follow-up period.

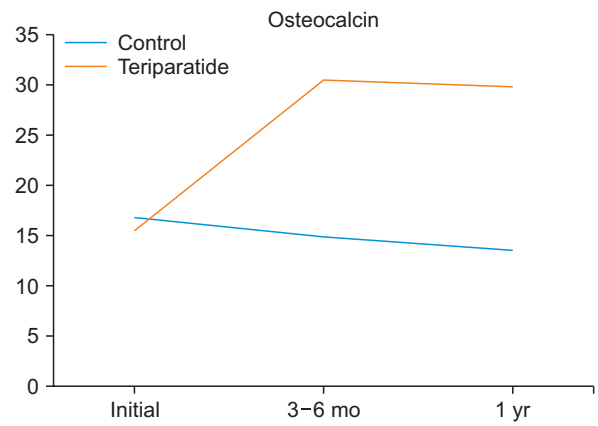

Fig. 3. Change of osteocalcin during 1-year follow-up period.

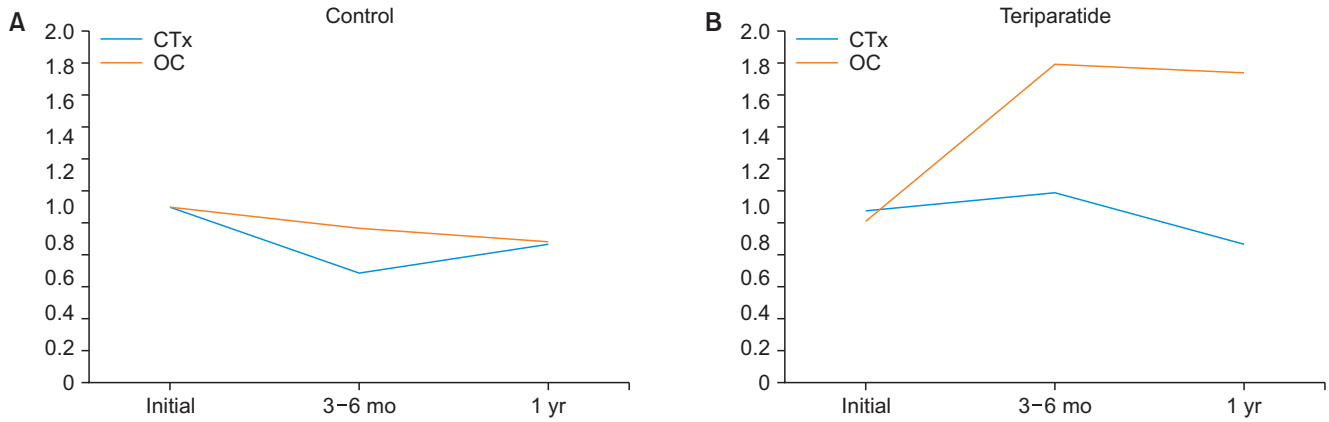

Fig. 4. Difference between the C-terminal telopeptide (CTx) and osteocalcin (OC) values in the control (A) and teriparatide (B) groups.

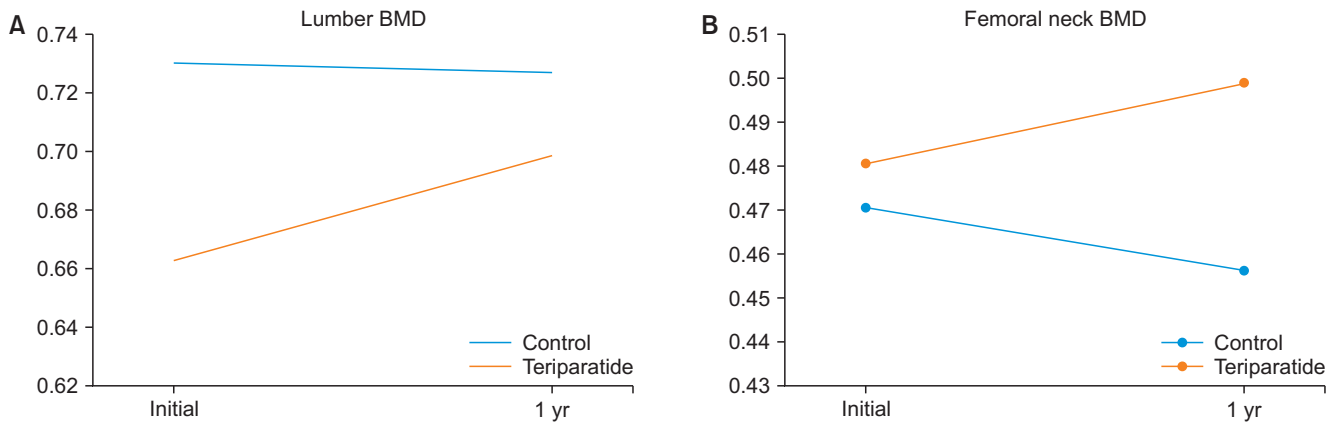

Fig. 5. Difference between the control and teriparatide groups in the lumber bone mineral density (BMD; A) and femoral neck BMD (B).

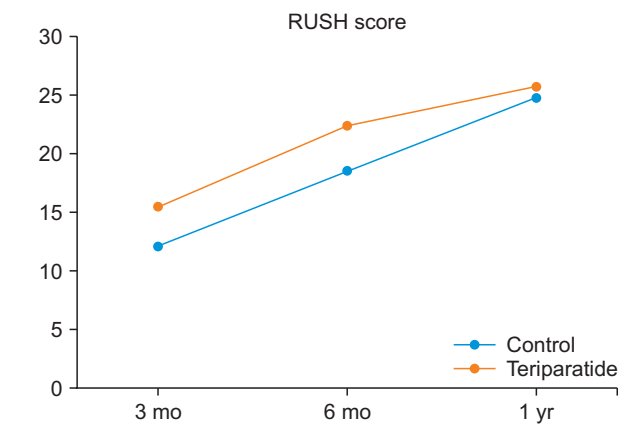

Fig. 6. Change of Radiographic Union Score for Hip (RUSH) score during 1-year follow-up period.

the initial femoral neck BMD (0.481), while the 1-year femoral neck BMD (0.456) of the control group decreased compared to the initial femoral neck BMD (0.471) (Fig. 5).

At 3 and 6 months, the mean RUSH scores showed significant differences between the control group and the teriparatide group. The mean RUSH score in the control group was 12.105 at 3 months and 18.571 at 6 months, while the mean RUSH score in the teriparatide group was 15.476 at 3 months (p = 0.004) and 22.389 at 6 months (p = 0.006). However, no significant difference in RUSH scores was found between the two groups at 1 year (p = 0.461) (Fig. 6).

DISCUSSION

PTH is an endocrine hormone that is well known for maintaining calcium homeostasis. Although PTH is a catabolic protein releasing calcium from the bone, it also has the anabolic effect of increasing bone mass in humans[9,13] and animals.[14,15] PTH has been shown to improve fracture healing, increase BMD, and reduce osteoporosis-related fractures.[10] Teriparatide, which is recombinant PTH, has been known to have efficacy in treating osteoporotic fractures, but its value in the treatment of fractures is de-

batable.[16] However, recently, the ability of teriparatide to stimulate bone formation processes before bone resorption in what is called the "anabolic window" has been studied.[17] Additionally, in some human trials, teriparatide appeared to enhance fracture healing.[18] In the present study, there were no statistically significant differences in CTx, OC, and lumbar and femoral neck BMD between the teriparatide group and the control group. However, OC tended to increase in the teriparatide group, and the lumbar and femoral neck BMD also tended to increase. This finding was meaningfully different from that in the control group, which tended to decrease in the present study. The evaluation of the rate of change in BMD over a year showed that L-BMD increased by more than 7% in the teriparatide group. In addition, RUSH scores in the teriparatide group were significantly high at 3 and 6 months. RUSH is a validated tool to improve agreement between radiologists and orthopedic surgeons in evaluating fracture healing.[19] Therefore, these findings suggest that weekly teriparatide use result in faster bone union in patients with osteoporotic hip fractures.

Because the CTX values in the teriparatide group gradually decreased and OC values remained high at 1 year, it seems that weekly administration of teriparatide increased BMD in the teriparatide group by the anabolic window effect. The anabolic window lasts about 18 to 24 months before bone resorption exceeds bone production and no net increase in bone mass can be obtained, limiting its therapeutic use to a maximum of 2 years.[20] In the present study, the anabolic window was observed in the teriparatide group. Therefore, the key findings of this study are that weekly teriparatide use improved fracture healing and bone formation and showed better clinical outcomes at 1 year after various types of hip fracture surgery.

The bone turnover markers are affected by fracture repair system and their rates of change depend on the kind of fracture and how long it takes for fracture healing.[21] OC is secreted from osteoblasts and plays an important role in bone mineralization and calcium ion homeostasis, and the level of serum OC level has been demonstrated to reflect the level of BMD when using bone formation drugs.[22] CTx is also extensively studied bone resorption biomarkers because of its sensitivity and quick reflection of bone recovery.[23] According to Veitch et al.,[24] OC was affected by tibial shaft fractures, then showed a slight decrease at the beginning, and then increased up to 24 weeks. It has also been reported that CTx values increased for 2 weeks after fracture and then decreased up to baseline.[25] Most changes in bone turnover markers take place in the first 6 months,[24] but the results of the present study showed high OC and low CTx compared to baseline at 1 year follow-up when weekly teriparatide use was applied. Procollagen type I N-terminal propeptide (PINP) also has an advantage as a bone formation marker, but has a disadvantage that it can increase up to 360 days due to fracture.[26]

Weekly injection of teriparatide is clinically available for anabolic therapy for osteoporotic fractures.[27] The weekly administration has several advantages compared to daily administration. Weekly administration can be more convenient for some patients who cannot move easily. In general, it is difficult for elderly patients to receive adequate care at home as they have difficulty walking or need personal care for underlying diseases or after orthopedic surgery. Many elderly nursing homes in South Korea provide food, clothing, and shelter and have medical personnel stationed to take responsibility for the health and care of the elderly. However, some of the elderly living in these nursing facilities have as much difficulty in moving as those who live alone or have diseases such as dementia. In addition, given that these nursing homes are located in rural areas rather than large cities, injection therapies such as teriparatide are inevitably a great challenge for patients residing in nursing homes with limited mobility and limited physical distance. Therefore, weekly large-dose administration is a necessary injection method for older people. In contrast, a study by Miyauchi et al.[28] demonstrated that the daily administration of teriparatide by self-injection showed high treatment compliance. These results suggest that daily self-injections with low-dose teriparatide might have more advantages for older people who need osteoporotic fracture treatment than weekly large-dose administration at a hospital. Further research that compares the efficacy differences between physician-administered weekly large-dose injection and low-dose self-injection is needed.

In conclusion, the present study evaluated the efficacy and practicality of weekly teriparatide injection as a treatment of older women with osteoporotic fractures. Weekly teriparatide use improved fracture healing and bone formation and had better clinical outcomes 1 year after hip fracture surgery by the anabolic window effect. However, weekly administration could have caused follow-up loss in older people. Further research is necessary to compare weekly teriparatide use with other teriparatides that can be applied daily by self-injection.

There were several limitations to this study. First, during the study period, adherence was not good. It is hard for patients to keep up with injections because they have to visit the hospital once a week. However, a cooperative system was established between local hospitals in

Gyeongsangnam-do, and requests were made to all internal medicine clinics through a telephone contact network. In addition, elderly patients with hip fractures were often hospitalized for 4 weeks in university hospitals and stayed in nursing hospitals they were transferred to for 3 months or more, so they were able to continue injections in the hospital. In patients treated with teriparatide, adherence could be increased through fluid and water intake and antiemetic treatment. However, during the study period, there were cases where follow-up was lost or it was not possible to visit the hospital for injections due to the coronavirus disease 2019 (COVID-19) pandemic outbreak. Second, there was much decrease in compliance due to non-serious adverse reactions, especially nausea and vomiting. In particular, 3 patients (2.33%) complained of discomfort due to side effects of the drug, albeit not serious, and withdrew from the study. Third, it was difficult to conduct long-term treatment. The patients had to visit the hospital every week for injections, but it was difficult for them to visit nearby hospitals after discharge under the Korean medical support policy. Moreover, due to the COVID-19 pandemic, many elderly people refrained from making frequent hospital visits for injections. Fourth, physical activity could not be accurately evaluated before treatment (only oral questionnaire was used) because there was a large difference in the degree of rehabilitation and nutrition after treatment among the patients.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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