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Compliance and discontinuation of denosumab treatment in postmenopausal Japanese women with primary osteoporosis or rheumatoid arthritis and osteoporosis

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ABSTRACT

Objectives: The aim of this study was to examine the discontinuation and occurrence of fracture during denosumab treatment in Japanese women with primary osteoporosis or rheumatoid arthritis (RA) with osteoporosis.
Methods: This retrospective study included 143 patients with primary osteoporosis and 96 patients with RA and osteoporosis who were treated with denosumab. Treatment discontinuation, fracture occurrence, lumbar spine (L1–4) bone mineral density (LS-BMD), and bilateral total hip BMD (TH-BMD) were examined before and at 1 and 2 years after treatment commencement.
Results: In the primary osteoporosis group, 32 cases dropped out and no fractures occurred from 0 to 1 year. Eighteen cases were lost to follow-up and no fractures were noted from 1 to 2 years. In the RA with osteoporosis group, 7 cases dropped out and no fracture occurred from 0 to 1 year. Twenty-one cases were lost to follow-up and 2 nonvertebral fractures were noted from 1 to 2 years. In this group, 13 cases dropped out from 1 to 2 years and 16 cases dropped out during the 2-year study period due to economic reasons. LS-BMD and TH-BMD values increased continuously for 2 years of treatment in both primary osteoporosis and RA with osteoporosis groups.
Conclusions: These results suggest that during denosumab therapy, the discontinuation rate is expected to remain low during 2 years of treatment in primary osteoporotic patients. In RA patients with osteoporosis, however, the discontinuation rate may increase due to economic reasons from 1 to 2 years of therapy.

1. Introduction

It is desirable to continue osteoporotic treatment until clinical goals are met since discontinuation and nonadherence to antiresorptive therapies have been associated with smaller decreases in bone turnover markers, more modest bone mineral density (BMD) gains, and an increased risk of fractures [1]. The continuation of osteoporotic therapies is therefore critical for fracture risk reduction.

Hadji et al. [2] recently described that the 2-year persistence of denosumab was 39.8%, which was 1.5–2 times higher than that for bisphosphonates (BPs), and that risk of discontinuation was significantly lower for denosumab than for BPs. Meanwhile, in rheumatoid arthritis (RA) patients, the risk of both vertebral and nonvertebral fractures accompanying osteoporosis is roughly double as compared with those in subjects without RA [3]. Thus, osteoporotic drugs are considered to be essential for fracture prevention in RA patients with osteoporosis as well, although the compliance of osteoporotic treatment in RA is quite low [3].

Treatment with denosumab causes a strong inhibitory effect on bone resorption markers [4]. Denosumab is also superior with respect to increased BMD and the prevention of both vertebral and hip fractures [5]. The treatment effects of denosumab persist for an extended time, even up to 8 years as reported by Papapoulos et al.

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[6]. Denosumab is a useful drug in BP-unresponsive primary osteoporosis as well [7]. Despite representing one of the best therapeutic options for osteoporotic patients, there are no reports on the long-term persistence of denosumab in patients with primary osteoporosis or secondary osteoporosis accompanying RA in Japan to date.

The aim of this study was to examine the discontinuation and occurrence of fracture during denosumab treatment in Japanese women with primary osteoporosis or RA with osteoporosis.

2. Materials and methods

In the primary osteoporosis group, 143 primary osteoporotic postmenopausal Japanese women (average age, 76.4 ± 0.9 years; average body mass index [BMI], 20.9 ± 0.3 kg/m^2) were retrospectively enrolled between October 2013 and September 2015 as out-patients at our institutions. Among them, 48 patients had taken BPs (alendronate, 17 cases; risedronate, 7 cases; minodronate, 20 cases; ibandronate, 4 cases) and 49 patients had received teriparatide prior to denosumab therapy (Table 1). In the RA with osteoporosis group, 96 patients with RA complicated with secondary osteoporosis (average age, 70.0 ± 0.8 years; average BMI, 20.9 ± 0.4 kg/m^2) were retrospectively enrolled. Among them, 63 patients had taken BPs (alendronate, 39 cases; risedronate, 21 cases; minodronate, 3 cases) and 16 patients had received teriparatide prior to denosumab therapy (Table 2).

The diagnosis of RA in this study was conducted in accordance with the 2010 American College of Rheumatology/European League Against Rheumatism classification system [8].

The inclusion criteria for the study were osteoporotic patients with low lumbar spine (L1–4) BMD (LS-BMD) and/or bilateral total hip BMD (TH-BMD) of less than −3.0 standard deviation. The exclusion criteria were the presence of chronic renal failure (estimated glomerular filtration rate <40 mL/min/1.73 m^2), bone metabolic disorder, or diabetes mellitus, all of which affected osteoporosis, along with fracture within 1 year prior to the study. The diagnosis of osteoporosis was made in accordance with the revised criteria established by the Japanese Society of Bone and Mineral Research [9].

Table 1
Patient characteristics prior to denosumab treatment the primary osteoporosis group (n = 143).

Characteristic	Value
Age, yr	76.4 ± 0.9
Body mass index, kg/m^2	20.9 ± 0.3
Osteoporotic medications before denosumab treatment	
Bisphosphonates	48
Alendronate	17
Risedronate	7
Minodronate	20
Ibandronate	4
BP pretreatment period, mo	4.2 ± 0.8
Teriparatide	49
Osteoporotic fractures during the first year	0
Osteoporotic fractures during the second year	0
Lumbar spine 1–4 BMD, g/cm^2	
Before	0.799 ± 0.01
At 1 year (percentage increase)	0.832 ± 0.02 (7.6% ± 0.9%***)
At 2 years (percentage increase)	0.847 ± 0.02 (10.4% ± 0.8%***)
Total hip BMD, g/cm^2	
Before	0.629 ± 0.01
At 1 year (percentage increase)	0.640 ± 0.01 (2.8% ± 0.6%***)
At 2 years (percentage increase)	0.676 ± 0.01 (5.0% ± 0.7%***)

Values are presented as mean ± standard error or number.
BP, bisphosphonate; BMD, bone mineral density.
***P < 0.001 compared with before treatment.

The patient characteristics prior to denosumab treatment are presented as mean ± standard error (Tables 1 and 2). We observed significant differences in age and TH-BMD between the groups (Table 3). There was no washout period during the switch from previous medications to denosumab in this study. Fifty-three patients did not take native or active vitamin D, while the remaining 90 patients took it during this study in the primary osteoporosis group (Table 1), while 39 patients did not take native or active vitamin D, while the remaining 57 patients took it during this study in the RA with osteoporosis group (Table 2).

BMD was measured using a dual-energy X-ray absorption (DXA) fan-beam bone densitometer (Lunar Prodigy; GE Healthcare Bio-Sciences Corp., Pis-cataway, NJ, USA) at the L1–4 levels of the posteroanterior spine and bilateral hips. BMD was examined before treatment administration and at 12 and 24 months. Values and percentage changes in BMD were determined for each time point, and comparisons were made between the groups by statistical analysis. The coefficient of variation of the BMD measurements at the lumbar spine and hips were 0.7% and 1.1%, respectively. Routine quality control was ensured using a phantom box. Fracture sites were avoided during the evaluation of BMD. TH-BMD was calculated as the average BMD of the right and left hips. Physicians interpreting the BMD assessments and DXA measurements and the laboratory staff performing the bone marker assays were blinded to the treatment groups.

This study was approved by the Institutional Ethics Committee of Shinshu University School of Medicine and Showa Inan General Hospital. Informed consent was obtained from all patients before interviews by attending physicians. Information was obtained via interview with each patient by the patient's physician. The methods were carried out in accordance with approved guidelines. The clinical trial registration number is NCT02156960.

3. Results

The number of patients who completed this 2-year investigation was 93 of 143 in the primary osteoporosis group and 68 of 96 in the RA with osteoporosis group. There were no differences between the characteristics of dropout patients.

In the primary osteoporosis group, 32 cases dropped out (22.4%) from 0 to 1 year for unknown reasons (12 cases), economic reasons (3 cases), dental treatment (2 cases), admission to a nursing home (5 cases), hospitalization for another disease (7 cases), transfer to another hospital (2 cases), and death (1 case) according to exit interviews with physicians when applicable. Consequently, 111 patients continued therapy into year 2 (Table 4). No osteoporotic fractures occurred during the first year. LS-BMD values before and at 1 year of treatment were 0.799 ± 0.01 g/cm^2 and 0.832 ± 0.02 g/cm^2, respectively, and those of TH-BMD were 0.629 ± 0.01 g/cm^2 and 0.640 ± 0.01 g/cm^2, respectively. Compared with baseline values, the percent change of LS-BMD at 12 months was +7.6% ± 0.9% (P < 0.001) and that of TH-BMD was +2.8% ± 0.6% (P < 0.001) (Table 1). These findings indicated high persistence at 12 months (77.6%), no fracture occurrence, and substantially improved BMD values from denosumab treatment. From 1 to 2 years of therapy, 18 cases dropped out (16.2%) due to unknown reasons (6 cases), admission to a nursing home (2 cases), hospitalization for another disease (2 cases), transfer to another hospital (3 cases), and death (5 cases). As a result, 93 patients completed denosumab therapy (Table 4). No fractures occurred during the second year. LS-BMD value at 2 years was 0.847 ± 0.02 g/cm^2 and that of TH-BMD was 0.676 ± 0.01 g/cm^2. Compared with baseline values, the percent change of LS-BMD at 24 months was +10.4% ± 0.8% (P < 0.001) and that of TH-BMD was +5.0% ± 0.7% (P < 0.001). From 0 to 2 years, a total of 50