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Association of Young Age with Bone Mineral Density Improvement with Denosumab Treatment in Patients with Osteoporosis

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Abstract

Introduction: Analysis of predictive factors for the improvement of bone mineral density (BMD) in response to osteoporosis treatment is critical. Several studies reported on the analysis of bone turnover markers as a predictive factor for the improvement of BMD; however, few studies reported on predictive factors other than bone turnover markers. Thus, this study aimed to analyze other predictive factors for distal radial BMD improvement in response to denosumab treatment among patients with osteoporosis.

Methods: We evaluated 133 patients with osteoporosis over a 24 month period. All patients received denosumab (60 mg) subcutaneously every 6 months. The BMD of the distal radius was assessed in all patients and serum concentrations of PINP and TRACP5b determined.

Results: Denosumab treatment resulted in a 3.3% increase, from baseline, in distal radius BMD at 24 months. The average BMD change at 24 months was not significantly changed in relation to gender or prevalent medication. The average BMD change at 24 months was negatively correlated with patient's age. Almost all the points of PINP and TRACP5b were not correlated with BMD except TRACP5b value at 24 months

Conclusions: We found that improvement of bone mineral density with denosumab treatment for osteoporosis is associated with young age of the patients. We recommend denosumab treatment for younger patients with osteoporosis.

Keywords Osteoporosis; Prediction; Age; Denosumab

Introduction

The number of patients with osteoporosis is expected to increase by approximately a quarter between

2010 and 2025 worldwide because of the increase in the elderly population; thus, the number of osteoporosis-related fracture cases will also increase [1,2]. Fractures cause pain and immobility in patients and could increase mortality, with hip fractures being associated with half of the deaths attributable to osteoporosis [2]. Bone mineral density (BMD) decreases with age in both women and men, but especially in women after menopause because of changes in sex hormone levels [3]. Other factors, including genetics, nutrition, body weight, muscle strength, and calcium absorption, are thought to play a significant role [4].

Assessment of the response to osteoporosis treatment requires the serial measurement of BMD, and analysis of predictive factors for the improvement of BMD is critical. In previous studies, both baseline and early changes in bone turnover markers have been reported to predict late BMD response [5-7].

Denosumab, a fully human monoclonal antibody, could improve BMD [8-10], thereby lowering the risk for fractures [11]. Clinical trials demonstrated that denosumab causes a rapid and significant decrease in the rate of bone turnover, which is associated with a significant increase in BMD [8,10,12-14] and a significant reduction in fracture incidence among postmenopausal women with osteoporosis [11].

We hypothesize that, in response to denosumab treatment, various factors other than bone turnover markers may influence BMD improvement. Only few studies investigated other predictive factors that contribute to BMD improvement. Hence, we analyzed other predictive factors for late BMD improvement with denosumab treatment.

Patients and Methods

Patients over the age of 60 years, treated for osteoporosis at our center (113 women and 20 men), were eligible for the study. The diagnosis of osteoporosis was based on the diagnostic criteria of primary osteoporosis in Japan [15]. The exclusion criteria were as follows: creatinine clearance <30 mL/min, corrected serum calcium level >11.0 mg/dL (2.8 mmol/L) or <8 mg/dL (2 mmol/L), active cancer, metabolic bone disease other than osteoporosis, dementia, and life expectancy of <6 months. An additional exclusion criterion for bone turnover marker assessment was any fracture at baseline. Eligible patients received denosumab (60 mg) subcutaneously every 6 months, in combination with a daily supplementation of 400 IU vitamin D throughout the study period.

Assessments

BMD was assessed by dual-energy X-ray absorptiometry (DXA) scans of the left distal 1/3 of the radius using a DTX-200 DexaCare Osteometer unit (MediTech, Inc., Signal Hill, CA, USA) at baseline and at 6, 12, 18, and 24 months. For patients who had sustained a previous fracture of the left wrist, the DXA scan was performed on the right side. Serum levels of PINP and TRACP5b, as markers of the rate of bone turnover at baseline and at 6, 12, 18, and 24 months, were measured in all patients.

All the data were obtained in accordance with the World Medical Association Declaration of Helsinki (ethical principles for medical research involving human subjects).

Statistical analysis

The percent change in BMD was calculated by dividing the BMD value at 6, 12, 18, and 24 months by the BMD value at baseline and multiplying the quotient by 100 (Figures 1, 2 and 3). Demographic data were recorded as the mean ± standard deviation, unless otherwise indicated. Changes in the measured variables over time were evaluated using a one-way analysis of variance, with a Tukey post hoc test for multiple comparisons of paired samples (Figures 1-3). Between-group comparisons were performed using the Mann-Whitney U test (Table 1).

The correlation between BMD and the following was evaluated using Pearson's correlation: age, PINP value at baseline, PINP value at 12 months, PINP value change from baseline to 12 months, TRACP5b value at baseline, TRACP5b value at 12 months, and TRACP5b value change from baseline to 12 months (Table 2). All analyses were performed using SPSS (IBM Corp., Armonk, NY, USA), with a p value <0.05 considered statistically significant.

		Age	PINP value base	PINP value 12M	PINP change 12M	TRAP value base	TRAP value 12M	TRAP change 12M
BMD value base	Correlation coefficient	-0.3	-0.03	-0.01	0.297	-0.15	-0.16	0.05
	p-value	<0.005	0.798	0.871	0.104	0.439	0.113	0.68
BMD value 24M	Correlation coefficient	-0.42	-0.08	-0.08	0.11	-0.19	-0.21	0.03
	p-value	<0.005	0.523	0.378	0.4	0.067	0.04	0.804
BMD change 24M	Correlation coefficient	-0.31	-0.13	-0.13	-0.01	-0.1	-0.1	-0.03
	p-value	<0.005	0.133	0.133	0.95	0.353	0.35	0.797

Table 1: Association between patient's age or bone turnover markers and bone mineral density.

Patients number	133
Age (years old)	77.8 ± 7.8
Sex	male 20, female 113
Prevalent fractures	Total 60/133 (45.1%)
Vertebral fracture	41
Femoral neck fracture	8
Other fractures	23
Prevalent medication	Total 43/133 (32.3%)
Bisphosphonate	23
Serm	6
Vit D	5
Bisphosphonate+Vit D	9
Pth	0

Table 2: Relevant patient characteristics at baseline.

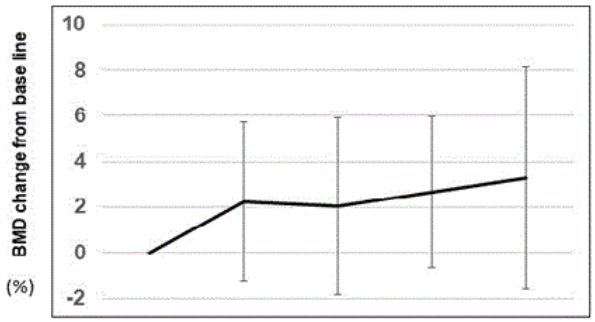

Figure 1: Percentage of BMD change from baseline.

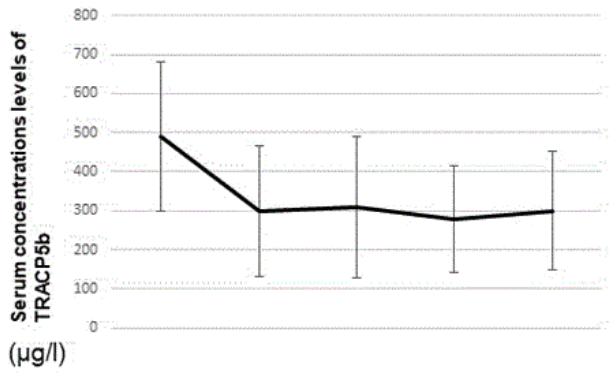

Figure 2: Serum concentration levels of TRACP5b.

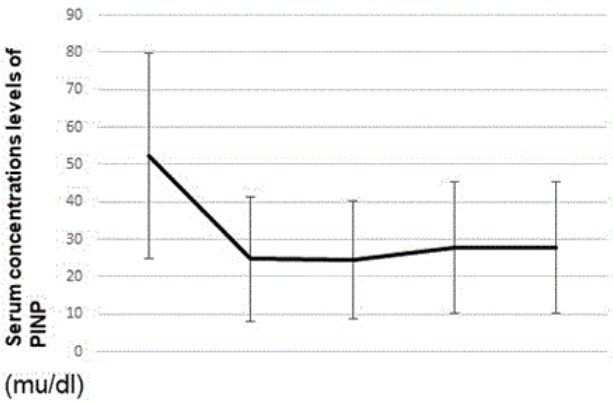

Figure 3: Serum concentration levels of PINP. The bars show the mean ± standard deviation (SD).

Ethics

The study protocol was approved by our institutional ethics committee on November 16, 2014 (No. 170136), and informed consent for participation in the study was obtained from all participants.

Results

Clinical background of our study sample

Clinical background data are summarized in Table 3. Of the 133 patients enrolled in the study, 120 had a clinical diagnosis of primary osteoporosis and 13 had secondary osteoporosis, 45.1% had a history of fracture and 32.3% were being treated with a primary osteoporosis drug other than denosumab (Table 3).

Change in the bone mineral density of the distal radius

The average BMD of the distal radius at baseline was 0.26 ± 0.05 g/cm^3, and a significant increase in BMD from baseline at all time-points of measurement was noted (Figure 1): 6 months, 2.2% (p<0.001); 12 months, 2.0% (p<0.001); 18 months, 2.6% (p<0.001); and 24 months, 3.3% (p<0.001).

		BMD value base	BMD value 24M	BMD change 24M
Gender	Male	0.334 ± 0.024	0.347 ± 0.069	3.9 ± 0.7
	Female	0.25 ± 0.057	0.259 ± 0.058	3.6 ± 0.6
	p-value	<0.001	<0.001	0.623
Prevalent medication	(+)	0.275 ± 0.059	0.286 ± 0.07	3.9 ± 1.2
	(-)	0241 ± 0.047	0.25 ± 0.058	3.7 ± 1.6
	p-value	0.001	0.004	0.789

Table 3: Association between patient's backgrounds and bone mineral density.

Bone turnover markers

The average concentration of TRACP5b was significantly lower by 60.8% at 6 months (p<0.001) and remained at this reduced level thereafter (Figure 2). A significant decrease in serum PINP concentration of 47.1%, relative to the baseline, at 6 months (p<0.001) was found, which remained at this reduced level thereafter (Figure 3).

Association between patient's backgrounds and bone mineral density

The relationship between BMD values and the patients' backgrounds are shown in Table 3. The average BMD values at baseline and at 24 months were higher in prevalent osteoporosis treatment groups (Table 3). However, the average BMD change at 24 months was not significant in relation to gender or prevalent medication (Table 3).

Association between patient's age or bone turnover markers and bone mineral density

The relationship between BMD values and age or bone turnover markers are presented in Table 2. The average BMD values at baseline and at 24 months were negatively correlated with age (Table 2). Further, the average BMD change at 24 months was negatively correlated with age (Table 2). Almost all the points of PINP and TRACP5b were not correlated with BMD except TRACP5b value at 24 months (Table 2).

Discussion

This study aimed to analyze the predictive factors for distal radial BMD improvement with denosumab treatment among patients with osteoporosis. Denosumab treatment improves BMD potentially via the suppression of bone resorption and formation [7,16]. Eastell et al. reported that serum CTX and PINP levels decrease at 6 months with denosumab treatment [7]. Nakamura et al. reported that a decrease in serum CTX and bone specific alkaline phosphatase levels was observed at 1 month with denosumab treatment. In this study, denosumab suppressed the serum levels of bone turnover markers, including PINP, at 6 months. Our results are consistent with previous reports [7,16].

Firstly, we analyzed the association of gender or prevalent medication with BMD increase. Peak bone mass, as measured by DXA, is greater in men than in women because of the larger bone size in men

and the fact that the two-dimensional depiction of BMD by DXA is influenced by bone size [17,18]; thus, the higher DXA-measured BMD in men is simply because of the larger bone size. Moreover, BMD values were higher in men even after treatment with denosumab; however, the BMD improvement in response to denosumab treatment between the men and women showed no significant difference.

Tsai et al. reported that switching from teriparatide to denosumab for an additional 2 years further increases BMD [19]. Sanchez et al. reported that a better response was observed in denosumab-treated group previously treated with bisphosphonate compared with the non-pretreated group and concluded that the discrepancy of the result could be attributed to the small number of the control group [20]. Bisphosphonates could also reduce bone resorption; however, the mechanism of action is different from that of denosumab. Denosumab has been shown to achieve greater increases in BMD compared with oral alendronate in anatomic regions with different percentage of trabecular and cortical bone especially in the distal radius [8,21]. These results supported our finding that no significant difference in distal radial BMD improvement between those with and those without prevalent medication exists.

Several studies reported on the analysis of bone turnover markers as a predictive factor for BMD improvement with denosumab treatment [16]. Tsai et al. reported that higher baseline levels of OC, P1NP, and CTX are associated with greater increases in BMD at the lumbar spine and total hip [16]. Decreased OC, P1NP, and CTX levels at 3, 6, and 12 months were also associated with greater increases in BMD, particularly at the spine [16]. However, the relationship between changes in distal radius BMD and bone turnover markers demonstrated that the decrease in serum OC or PINP level is not associated with a greater increase in BMD, whereas decreased CTX level was associated with a greater BMD increase at 3 and 12 months [16]. Hence, predicting BMD increase in the distal radius with denosumab treatment based on bone turnover markers appears challenging. Our results were consistent with previous studies [16].

Furthermore, only few reports on the analysis of predictive factors for late BMD increase other than bone turnover markers exist [22,23]. Cheng et al. reported that young age is related to BMD changes with denosumab treatment in chronic kidney diseases patients; they demonstrated that the effect of the RANKL inhibitor could be correlated with age and that younger patients showed a more potent inhibitory effect [22]. Anastasilakis et al. reported on the analysis of microRNA (miR) expression change in response to denosumab treatment [**23**]. The expression levels of miR-21-5p, miR-23a-3p, miR-26a-5p, miR-27a, miR-222-5p, and miR-335-5p were changed after denosumab treatment [23]. However, no association between BMD change and the relative expression of microRNAs at any time point was noted [23]. We demonstrated that young age is associated with BMD improvement with denosumab treatment at 24 months, and we speculate that the mechanism of such improvement may be similar to that previously reported [22].

There are several limitations in our study that need to be acknowledged. First, we demonstrated that young age was associated with BMD improvement with denosumab treatment. However, the finding was not in consideration of other factors including prevalent medication for osteoporosis. Second, the measurement of BMD was only performed for the distal radius, due DXA scanner used. Future analyses are required to clarify our findings.

Conclusion

To our knowledge, this is the first study to demonstrate the association between BMD improvement with denosumab treatment for osteoporosis and young age of patients. We recommend denosumab treatment for younger patients with osteoporosis.

Funding

This research was not supported by a grant.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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