Denosumab Treatment Improved Health-Related Quality of Life in Osteoporosis: A Prospective Cohort Study

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ABSTRACT
Improving patient health-related quality of life (HRQOL) and prevention of bone fracture are important components of the treatment of osteoporosis. Our aim in this study was to evaluate the effect of denosumab treatment in improving HRQOL among patients with osteoporosis. Our analysis was based on 332 patients with osteoporosis, followed for 24 months. All patients received denosumab (60 mg) subcutaneously every 6 months. Bone mineral density (BMD) was assessed at the distal radius, with serum concentration of calcium, phosphate, P1NP, and TRACP5b also measured. HRQOL assessment included pain (visual analogue scale [VAS]) and the EQ-5D questionnaire. A multivariate analysis was performed to identify the possible confounders associated with deterioration in the EQ-5D utility score in response to denosumab treatment. Denosumab treatment yielded a 3.4% increase in BMD at 24 months. Serum levels of TRACP5b and P1NP decreased significantly, from baseline, at 6 months, with no effect on calcium and phosphate levels. Pain VAS and EQ-5D utility score improved significantly, from baseline, at 6 months, with the EQ-5D utility score correlating with the BMD at all time points of measurement over the 24-month period of observation. Knee osteoarthritis and multiple comorbidities were significantly associated with a worse HRQOL in response to denosumab treatment. Denosumab treatment increased BMD, with improvements in BMD correlating with improved HRQOL, supporting a possible benefit of using denosumab for the treatment of osteoporosis. © 2019 The Authors. JBMR Plus published by Wiley Periodicals, Inc. on behalf of American Society for Bone and Mineral Research.

KEY WORDS: DENOSUMAB; DXA; OSTEOPOROSIS; QOL

Introduction
Osteoporosis is a major public health concern worldwide. The number of patients who sustain a hip fracture is predicted to increase by 50% by the year 2050 as the elderly segment of the general population in Asia continues to increase. Because osteoporosis increases with age, it is further expected that the incidence and costs related to osteoporotic fractures will also increase by 50% over the next two decades. After menopause, the expression of nuclear factor kappa-B (RANK) ligand, an essential mediator of osteoclast formation and activation, increases, which results in increased bone resorption and can lead to osteoporosis. The fully human monoclonal antibody, denosumab, is associated with improvements in bone mineral density (BMD) and reductions in fracture risk. Denosumab (Prolia; Amgen Inc., Thousand Oaks, CA, USA) is a decoy receptor of RANK ligand that exerts effects at both trabecular and predominantly cortical bone regions. Clinical trials, including the FREEDOM trial, have shown that denosumab causes a rapid and significant decrease in bone turnover rate, which is associated with significant increases in BMD and significant reductions in fracture risk in postmenopausal women with osteoporosis.

Dual-energy X-ray absorptiometry (DXA) is widely used to help assess and follow the risk of fracture in individual patients and to monitor therapeutic intervention. Repeating DXA measurements can identify bone loss, monitor for disease progression, and assess response to treatment over time. Therefore, further description of the effect of denosumab on BMD at key skeletal sites is of relevance to all involved in the care of patients with osteoporosis and in the evaluation of treatments for this condition.

Improving of patient quality of life (QOL) as well as prevention of bone fracture is important for the treatment of osteoporosis. There were several reports that the osteoporosis treatment improved lower back pain and QOL among patients with osteoporosis-related back pain, with these improvements being associated with an increase in bone mass, via inhibition of bone resorption, and preventing bone fracture. Panico et al. reported that the use of teriparatide in patients with severe osteoporosis offered greater prevention against...
fractures, as well as greater improvement in QOL than bisphosphonates. Based on their randomized control trial on the short-term effects of alendronate and elcatonin on pain and QOL among patients with osteoporosis, lwamoto et al.\(^{(21)}\) concluded that alendronate suppressed bone turnover, reduced back pain, and improved QOL to a greater extent than elcatonin treatment. However, analysis of QOL improvement among patients with osteoporosis treated using denosumab has not been reported. Our guiding hypothesis for this study was that treatment of osteoporosis, using denosumab would also improve patient QOL and BMD. Therefore, the purpose of this study is to clarify the effect of denosumab treatment for osteoporosis on both BMD and QOL.

**Patients and Methods**

A total of 345 patients were enrolled in this study. We excluded 13 patients (3.8%) because these patients did not complete the 2-year follow-up period. Therefore, data from 332 patients were included in the analysis. Our sample of eligible participants include 288 women and 44 men with osteoporosis, ≥ 60 years of old. Of these, 185 patients were newly diagnosed with osteoporosis. The diagnosis of osteoporosis was made according to diagnostic criteria of primary osteoporosis in Japan.\(^{(22)}\) Eligible participants were screened on the following exclusion criteria: a calculated creatinine clearance of less than 30 ml per minute; a corrected serum calcium level of more than 11.0 mg/dL (2.8 mmol/L) or less than 8 mg/dL (2 mmol/L); active cancer; metabolic bone disease other than osteoporosis; dementia; a life expectancy of less than 6 months, and other factors based on the investigator’s judgment. The patient who was under treatment of fracture was excluded from this study. The denosumab treatment consisted of a 60 mg dose, injected subcutaneously, at a 6-month interval, combined with a daily dose of 400 IU vitamin D throughout the 24-month study period. This daily dose of vitamin D is recommended in the package insert for denosumab treatment.

Background of the patients that the evaluation of both markers and QOL was done is summarized in Table 1. As previously mentioned, the 152 patients were eligible for enrollment into our QOL study. Of these, 141 had a diagnosis of primary osteoporosis and 11 of secondary osteoporosis, 53.3% had a past history of fracture, and 71.7% had existing comorbidities. With regard to past treatment, 44.7% of patients were switching from a previous osteoporosis drug treatment.

**Assessments**

BMD was assessed by DXA scanning (DTX-200 DexaCare Osteometer; MediTech, Inc., Signal Hill, CA, USA) of the left distal 1/3 of the radius, obtained at baseline, and at 6, 12, 18, and 24 months during the treatment period. Of note, for patients with a left distal radius fracture, DXA measures were obtained on the right side.

Serum levels of bone turn over markers (serum calcium, phosphate, P1NP, and TRACP5b) were measured in 152 patients, at baseline and at 6, 12, 18, and 24 months. QOL of life was assessed in this study subgroup, at the same time points as serum levels. The QOL assessment included pain (measured using the visual analogue scale [VAS]) and the EQ-5D questionnaire. The EQ-5D questionnaire evaluates health status on the following five dimensions: mobility, self-care, performance of usual activities, pain or discomfort, and anxiety or depression. Each of these five dimensions are assessed on using a three-point scale, with the following descriptors: “no problem,” “some problem,” or “extreme problem.” Based on these five-dimensional scores, a health utility score (the EQ-SD utility score) is calculated, ranging between −0.594 (corresponding to the worst health state) and 1 (corresponding to the perfect health state).\(^{(23)}\) The VAS pain score was measured on a 10-point scale, and included upper back, lower back, and joint pain.

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**

BMD changes were calculated by dividing each BMD value at 6, 12, 18, and 24 months by the baseline BMD value and multiplying the quotient by 100 (Fig. 1). Demographic data were recorded as the mean ± standard deviation (SD), unless otherwise indicated. Statistical analysis was performed using one-way analysis of variance, with Tukey post hoc test for multiple comparisons of paired samples (Figs. 1 and 2). The association between BMD values and the EQSD utility score was evaluated using Pearson’s correlation (Table 2). To identify the possible confounders associated with a deteriorating of EQSD utility score in response to the denosumab treatment, patients were classified into two groups, those with an improvement in the EQ-SD score and those without an improvement. A multivariate analysis was used to evaluate the association between ‘no improvement’ in the EQ-SD utility score and other factors.

**Table 1. Relevant patient characteristics at baseline**

| Patients number (N) | 152 |
|---------------------|-----|
| **Age (years), mean ± standard deviation** | 76.3 ± 7.7 |
| **Sex** | male 25, female 127 |
| **Prevalent fractures** | 81 (53.3% of the total study sample) |
| vertebral fracture | 57 |
| femoral neck fracture | 10 |
| other fractures | 14 |
| **Prevalent medication** | 68 (44.7% of the total study sample) |
| bisphosphonate | 28 |
| SERM | 2 |
| Vit D | 19 |
| bisphosphonate + Vit D | 17 |
| PTH | 2 |
| **Comorbidity** | 109 (71.7% of the total study sample) |
| hypertension | 25 (22.9%) |
| liver dysfunction | 4 (3.7%) |
| heart disease | 7 (6.4%) |
| chronic renal failure | 4 (3.7%) |
| cancer | 9 (8.3%) |
| diabetes mellitus | 16 (14.7%) |
| osteoarthritis | 33 (30.3%) |
| multi comorbidity | 27 (24.8%) |
score and the following factors: BMD at baseline; prevalent spinal or hip fractures; prevalent use of osteoporosis medication; and comorbidities (including hypertension, liver dysfunction, heart disease, chronic renal failure, cancer, diabetes mellitus, knee osteoarthritis, and multiple comorbidities). For significant factors, the odds ratio (OR) and the corresponding 95% confidence interval (95% CI) were calculated. All analyses were performed using SPSS software (IBM Corp., Armonk, NY, USA), with a $P$ value $< 0.05$ considered significant.

**Ethics**

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

Results

Denosumab increased BMD of the distal radius

The average BMD of the distal radius at baseline was 0.29 g/cm³, with a significant increase, from baseline, at 6 months, and throughout the remainder of the period of observation, as follows (Fig. 1A): 2.3% increase at 6 months (P < 0.001), 2.4% at 12 months (P < 0.001), 2.5% at 18 months (P < 0.001), and 3.4% at 24 months (P < 0.001).

Bone turnover markers

The average serum concentration of calcium and phosphate was maintained, thereafter, throughout the study period (Fig. 1B). Denosumab treatment was associated with a significant decrease in the serum PINP concentration at 6 months (P < 0.001; Fig. 1D).

Denosumab treatment improved health-related QOL

The average pain VAS score was significantly decreased with denosumab treatment, from 3.5 at baseline to 2.7 at 6 months (P < 0.001; Fig. 2A). The average EQ-5D utility score significantly increased over the same period, from 0.57 at baseline to 0.61 at 6 months (P = 0.007; Fig. 2B). Therefore, denosumab treatment improved health-related QOL (HRQOL).

Association between improvements in HRQOL and BMD

The correlation between BMD values and the EQ-5D utility score, at all time points of measurements, are reported in Table 2. The EQ-5D utility score was significantly correlated to the BMD value at most time points, indicative that an increase in BMD increased HRQOL.

Denosumab treatment did not improve HRQOL in patients with knee osteoarthritis and multiple comorbidities

No association was observed between the change in the EQ-5D utility score and the baseline BMD value, prevalent use of osteoporosis medication, or prevalent fracture. However, a deterioration in the EQ-5D during the treatment period was associated with knee osteoarthritis (OR, 3.1; 95% CI, 1.1 to 9.2) and the presence of multiple comorbidities (OR, 5.5; 95% CI, 1.8 to 16.6; Table 3).

Discussion

The purpose of this study was to clarify the effect of denosumab treatment for QOL improvement in osteoporosis patients. We demonstrated that denosumab treatment increased BMD of distal radius and improved HRQOL. Bolognese et al. (24) similarly reported an increased in BMD with denosumab treatment in a sample of 441 women, with an increase, from baseline, of 7.7% in the spine and 4.0% in hips, as well as a 1.9% increase in the distal radius BMD at 24 months. Another study similarly reported a 2.2% increase in the distal radius BMD at 24 months. (25) Our increase in the distal radius BMD of 3.4% at 24 months is higher than previously reported rates of BMD increase. This higher rate of BMD increase in our study can be largely explained by the higher average age of our study group (78.1 years), compared to an average age of 73 years and 59 years in these previous studies. As such, the average distal radius BMD was lower at baseline in our study (0.29 g/cm³) compared to 0.37 g/cm³ in a previous study. (25) Differences in baseline BMD could affect the rate of change in BMD with treatment.

Denosumab potently suppresses bone resorption and formation. (26, 27) Eastell et al. (27) demonstrated that both the 6-month decrease in CTX and 6-month decrease in PINP were associated with the 36-month increase in BMD of the lumbar spine and hip. In our study, denosumab treatment suppressed serum levels of bone turnover markers, even PINP, but did not decrease serum levels of calcium and phosphate at 6 months, from baseline. These results are consistent with previous reports. (27)

Previous studies have reported a decrease in pain with osteoporosis treatment. (19, 28, 29) A previous study reported a decrease in VAS pain score between 2 and 4 weeks after the start of treatment using bisphosphonate. (28) Other studies have reported on the increase in CTX and 6-week decrease in P1NP were associated with the 36-month increase in BMD of the lumbar spine and hip. In our study, denosumab treatment suppressed serum levels of bone turnover markers, even PINP, but did not decrease serum levels of calcium and phosphate at 6 months, from baseline. These results are consistent with previous reports. (27)

Table 2. Correlation between bone mineral density and the EQ-5D utility score

| Covariate | Correlation coefficient | p-value | 6 M | 12 M | 18 M | 24 M |
|-----------|------------------------|---------|-----|-----|-----|-----|
| Baseline  | 0.23                   | 0.010   | 0.27| 0.13| 0.27| 0.26|

Table 3. Risk factors associated with a deterioration of the EQ-5D utility score

| Covariate                        | p-value | odds ratio | 95% CI   |
|----------------------------------|---------|------------|----------|
| Osteoarthritis                   | 0.046   | 3.1        | 1.1-8.8  |
| Multiple comorbidities           | 0.003   | 5.5        | 1.8-16.6 |

95% CI, 95% confidence interval
patients with knee osteoarthritis. Other studies have identified previous spinal fractures and comorbidities as factors associated with low health utility. Guillemin et al. showed that a higher number of comorbidities was associated with a reduced HRQOL. These reports supported our findings that the existence of knee osteoarthritis and multiple comorbidities reduced HRQOL, Regardless of of denosumab treatment. However, in our study group, prevalent fractures did not affect the improvement in HRQOL with denosumab treatment. Of note, however, is that prevalent fractures do contribute to a reduced HRQOL, and that denosumab treatment improves HRQOL outcomes in patients with fractures.

The limitations of our study should be acknowledged in the interpretation of findings. First, this is a noncomparative study, without a control group. Second, the measure of BMD was only performed at one site, the distal radius. There is a need for further analysis of the interaction between HRQOL and the BMD of the spine and femur/hip.

Regardless of of these limitations, we demonstrated that denosumab treatment increased the BMD of the distal radius and improved HRQOL. Moreover, the improvement in HRQOL correlated significantly with the increase in BMD with treatment. Our findings provide support for the use of denosumab for the treatment of osteoporosis.

Disclosures

All authors do not have any conflict of interest.

Acknowledgments

Authors’ roles: Study design: SHaya Data collection: SHaya, FK, TM, NC, SK, YM, YS, SSHashi, TM, TK, TN; Data interpretation: SHaya, TM; Statistics: YS; Drafting article: SHaya; Critical review: RK; Final approval: RK

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