
Manuscript Type: Original Article

Title: The effectiveness of denosumab in the treatment of postmenopausal osteoporosis
Running Title: Denosumab in the treatment of postmenopausal osteoporosis

Authors: Berke Aras, Ömer Kuzu

Institutions: 1Kastamonu Rehabilitation Centre, Kastamonu, Turkey

Address for Correspondence: Berke ARAS. Kastamonu Rehabilitation Centre, Kastamonu/Turkey

E-mail: drberkearas@gmail.com

Abstract

Objective: The purpose of the study was to demonstrate the efficiency of denosumab used in treatment of postmenopausal osteoporosis and to determine whether osteoporosis drug use before denosumab and the duration of denosumab use have an impact on the success of the treatment.

Methods: This study included 116 patients who were diagnosed with postmenopausal osteoporosis and treated with denosumab. The patients were grouped as those who had used regular oral bisphosphonate before denosumab treatment (n:88) and who had not used regular oral bisphosphonate before denosumab treatment (n:28). The outcome measures were the L1-L4 lumbar vertebra and total femur and femur neck T-scores and bone mineral density (BMD). All patients were evaluated pre-treatment, then at 1 and 2 years after treatment.

Results: Significant improvements were obtained in both groups in total vertebral BMD and T-scores, total femur and femur neck BMD and T-scores at 1 year after treatment. The total lumbar vertebra BMD and T-scores were statistically significantly increased in group not using regular oral bisphosphonates compared to the group using regular oral bisphosphonates. The use of denosumab treatment for two years was determined to have significantly increased the total femur and femur neck BMD and T-scores compared to the use of denosumab treatment for one year.

Conclusion: Denosumab is an effective treatment for postmenopausal osteoporosis. Further randomized controlled studies are needed on the effectiveness of long-term use of denosumab treatment and prior bisphosphonate use.

Keywords: Osteoporosis, postmenopausal, denosumab, oral bisphosphonates

Introduction

Osteoporosis is a systemic skeletal disease characterized by increased bone fragility as a result of decreased bone mass and deterioration of the micro-architectural structure of bone tissue. (1). Postmenopausal osteoporosis is common osteoporosis type, as estrogen deficiency causes to
increased bone turnover with bone resorption. Consequently, fractures can be seen as a result of spontaneous or low-energy trauma due to deterioration of the bone quality. The most common fracture locations are the vertebrae, proximal hip and wrist. (2). Osteoporosis and subsequent fractures are a crucial source of morbidity and mortality, and some of the patients who sustain an osteoporotic hip fracture do not regain their pre-fracture functional capacity (3). In addition to the fracture risk, osteoporosis has also been reported to negatively affect the quality of life of the patients (4).

In the pharmacological treatment of osteoporosis, drugs that inhibit bone resorption and stimulate bone formation are used (2). Bisphosphonates that inhibit bone resorption through osteoclast cells are widely used in the first-line treatment of osteoporosis. Denosumab, another therapeutic agent that inhibits bone resorption, is a human-derived monoclonal antibody against the receptor activator of nuclear factor-B ligand (RANKL). As a result of its high affinity for RANKL, which has an important role in the function of osteoclasts, it prevents the binding of RANKL to its ligand and disrupts the function and formation of osteoclasts, resulting in reduced bone loss (5). It is approved by the FDA for the treatment of postmenopausal osteoporosis with a high risk of fractures. In studies of patients with postmenopausal osteoporosis, it has been reported that the rate of hip fractures, vertebral and non-vertebral fractures is decreased with denosumab treatment (6). In a meta-analysis comparing the effect of denosumab and oral bisphosphonates in postmenopausal osteoporosis, it was reported that denosumab significantly increased bone mineral density (BMD) of the lumbar spine, total hip, femoral neck, and 1/3 radius compared to bisphosphonates (7).

The aim of the study was to present the results of denosumab treatment of postmenopausal osteoporosis in a rehabilitation center over a 3-year period.

Material and Methods
Study Design and Participant
A retrospective evaluation was made of the medical records of patients who received denosumab treatment in our rehabilitation center for postmenopausal osteoporosis between January 2018 and January 2021. The patients included in the study were those who treated with 60 mg subcutaneous
denosumab treatment for 6 months due to postmenopausal osteoporosis with low total femur/femur neck and/or lomber vertebra BMD (less than -2.5 SD) and who had annual bone mineral density follow-up examinations. Patients who did not take denosumab regularly or who did not attend an annual BMD examination were excluded from the study. The patients’ clinical osteoporosis risk factors (age, gender, smoking, alcohol use, low body mass index, family history of fracture, secondary osteoporosis causes) were evaluated. The past records of the patients were also reviewed and those with osteoporosis types other than postmenopausal osteoporosis (premenopausal, senile, juvenile) and patients with secondary osteoporosis causes (hypothyroidism, gastrointestinal disorders, rheumatological or hematological disorders, chronic renal or hepatic disease, alcoholism, metabolic bone disease, intake of drug influencing bone metabolism) were also excluded from the study. Demographic and clinical data, the duration of denosumab use, the history of osteoporosis drug use before denosumab, and unresponsiveness or intolerance to oral bisphosphonates were recorded.

In all patients, at the beginning and at the end of the 12/24-month follow up, BMD was measured using dual X-ray absorptiometry (DMS Imaging, Stratos DR, Grassobbia BG, Italy). The L1-L4 lumbar vertebrae and total femur and femur neck BMD and T-scores were recorded. The patients with a T-scores of -2.5 standard deviation and under were defined as having osteoporosis.

Although denosumab is a frequently used drug in the treatment of postmenopausal osteoporosis in Turkey, there are some requirements for reimbursements from national healthcare funding. In order to provide patients with denosumab therapy, reimbursement is possible if patients are either unable to tolerate oral bisphosphonates or are unresponsive to oral bisphosphonate therapy before the use of denosumab. Therefore, the patients included in this study comprised one group that had been unresponsive to regular oral bisphosphonate treatment for at least 1 year, and another group who could not tolerate oral bisphosphonates for gastrointestinal reasons after the first dose.

Patients on denosumab treatment were also grouped according to how many years they had been treated. Patients with data for only 1 year (12 months) and patients with data for two years (24 months) were divided into two groups. BMD and T-scores at 0 and 12 months for patients with one-year data and at 0 and 24 months for patients with two-year data were analyzed.
Ethic approval
This study has been prepared in accordance with the principles of the Helsinki Declaration. The protocol of the study was approved by the Local Ethics Committee (Kastamonu Training and Research Hospital 28.01.2021/KAEK-143-25).

Statistical analyses
Statistical data analyses were performed with SPSS for Macbook 20.0 software (SPSS Inc. USA). Descriptive data were displayed as mean ± standard deviation values for continuous variables and as number and frequencies for categorical variables. Normal distribution of the patient’s data was evaluated with the Kolmogorov-Smirnov test. The intra-group variations in BMD changes from pre-treatment to post-treatment were analyzed with the related samples Wilcoxon signed-rank test. In the inter-group comparisons, the changes of the parameters evaluated with the Mann-Whitney U test. P <0.05 was determined as statistical significance.

Results
Evaluation was made of the records of 152 patients who received denosumab treatment for a diagnosis of postmenopausal osteoporosis. A total of 36 patients were not eligible for the study; 21 patients due to lack of annual BMD records and 15 patients due to secondary osteoporosis (rheumatic disease, hyperthyroidism, etc.). Flow chart of the study is shown in Figure-1.

The mean age of the patients was 65.7± 8.8 years and the mean body mass index was 22.4± 2.2 kg/m². Denosumab was used by 28 patients (24.1%) because they could not tolerate oral bisphosphonates, and 42 patients (36.2%) had used alendronate and 46 (39.7%) had used ibandronate for at least 1 year and did not benefit from the treatment. One-year results were available for 88 patients (75.8%) and two-year results for 28 (24.1%).

After the treatment, improvement was observed in 84 (72.4%) total femur and femur neck BMD scores and in 101 (87.0%) total lumbar vertebra BMD scores. Compared to pre-treatment, statistically significant improvements were observed in the post-treatment total vertebral BMD and T-scores, and total femur and femur neck BMD and T-scores (Table-1).
When the patients were grouped according to regular oral bisphosphonate use before denosumab treatment, it was observed that the total lumbar vertebrae T-scores and BMD were statistically significantly increased in the group not using regular oral bisphosphonates compared to the group using regular oral bisphosphonates. No significant difference was determined between the groups in respect of the total femur and femur neck BMD and T-scores (Table-2).

When the patients were grouped according to the duration of denosumab use, the change in total femur and femur neck BMD and T-scores in the group using denosumab treatment for two years was observed to have increased significantly compared to the group using denosumab treatment for one year. No significant difference was determined between these two groups in respect of the changes in total lumbar spine BMD and T-scores (Table -3).

Throughout the study, no serious side-effects were observed after treatment.

Discussion

In this study, the results of patients who used denosumab for postmenopausal osteoporosis in a rehabilitation hospital for 3 years were examined. At the end of the study, positive improvements were observed in lumbar and femur BMD and T-scores after the use of 60 mg denosumab every 6 months. When the patients were grouped according to the duration of treatment, there were seen to be more significant improvements in the total femur and femur neck BMD and T-scores of the patients using denosumab for two years. When the patients were grouped according to previous oral bisphosphonate use, the lumbar BMD and T-scores were more significant in the group who had not previously used oral bisphosphonates.

In the 3-year phase-3 Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) (6) and 7-year FREEDOM extension (8) studies conducted on the use of denosumab in the treatment of postmenopausal osteoporosis, there was determined to be a rapid decrease in bone turnover markers immediately after the subcutaneous administration of 60 mg denosumab and they started to increase again after 6 months. Unlike bisphosphonates, denosumab is not incorporated into the bone, so its effect on bone turnover markers, BMD, and histomorphometric measurements is reversible (9-11). In a previous study, it was shown that iliac bone biopsies performed in patients using denosumab had no adverse effects on bone.
mineralization, lamellar bone formation and bone microarchitecture (12). Therefore, in this retrospective study, patients were excluded if they did not use denosumab subcutaneous injections regularly for 6 months. According to the study results, positive improvements were observed in the BMD and T-scores of all the patients.

In the European guideline for the diagnosis and management of postmenopausal osteoporosis published in 2019, oral bisphosphonates (alendronate, risedronate, ibandronate) are the first-line therapy for most patients in pharmacological treatment, but in patients who cannot tolerate oral bisphosphonates; i.v. bisphosphonates and denosumab are recommended. Other alternative pharmacological treatment options are; hormone replacement therapy and raloxifene. Teriparatide is recommended in patients with high fracture risk (1). Studies on combination or sequential drug use still do not provide sufficient data on the incidence of fracture prevention. The most accepted view is that the treatment of anabolic drugs such as teriparatide is limited to 18-24 months and the effect decreases when the treatment is stopped, so it should be continued with an anti-resorptive drug (bisphosphonate, denosumab, etc.) at the end of the treatment (13-14).

In the literature, there are controlled studies comparing denosumab and bisphosphonates in the treatment of postmenopausal osteoporosis. Denosumab has been shown to have more significant improvements in total hip, lumbar vertebrae, trochanter, and radius BMD scores compared to weekly alendronate (15,16) and monthly ibandronate (17) and risedronate (18) treatments. In another study of patients who had used oral bisphosphonate treatment before, it was reported that denosumab achieved more significant results in total vertebrae, total hip and radius BMD scores compared to zolendronic acid (19). In another study, conducted with minodronate, which is a third generation bisphosphonate and known as the strongest bisphosphonate, more significant improvements were found in BMD and bone turnover markers in the group that switched from minodronate to denosumab treatment compared to the group that continued to use minodronate (20). In a meta-analysis of 5361 patients by Lyu et al, in which denosumab and bisphosphonates were compared, it was concluded that denosumab increased the total hip, femoral neck, and total lumbar vertebrae BMD scores more (21). The reason why denosumab causes more significant improvements compared to bisphosphonates is thought to be that the mechanism of action of denosumab is different from that of bisphosphonates and the bone remodeling process starts earlier.
(22). Similarly, in the current study, statistically significant improvements were observed in the BMD data of the patients using denosumab treatment because they were unresponsive to oral bisphosphonate therapy.

It is controversial whether the use of bisphosphonates prior to denosumab treatment has an effect on the treatment. In a study conducted by Nakamura et al on patients with rheumatoid arthritis, positive effects were found in the BMD scores in groups that both used and did not use bisphosphonates before denosumab, and there was no significant difference between the groups, although bone turnover markers were found to be significantly more suppressed in the group that had not previously used bisphosphonates (23). On the other hand, in a study conducted by Suzuki et al in which the effect of long-term use of bisphosphonates before denosumab treatment was examined, it was concluded that lumbar BMD scores were significantly more improved in the group that did not receive bisphosphonates before denosumab (24). In addition, it was concluded that the change in bone turnover markers was more pronounced in the group that was not previously treated with bisphosphonates after treatment. In present study, more significant improvements were found in the lumbar spine BMD and T-scores in the group of patients using denosumab because they could not tolerate oral bisphosphonates after the first dose, compared to the group using regular oral bisphosphonates for at least 1 year. However, it is not known how the previously used bisphosphonate affects denosumab, but it is likely to be related to changes in the remodeling area and degree of mineralization as reflected by bone markers.

In the FREEDOM extension study showing the long-term effects of denosumab, it was shown that improvements in the BMD scores of patients continued for up to 10 years with no evidence of plateau. (9). The 2-year DIRECT trial and its 1-year extension trial were consistent with these findings (25). Similarly, in the present study, more significant improvements were found in the total femur and femur neck BMD and T-scores of the patient group using denosumab for two years (24 months) compared to the group using denosumab treatment for one year (12 months). Denosumab, as an immunoglobulin, is expected to be reduced to peptides and amino acids independent of hepatic metabolism. Therefore, denosumab pharmacokinetics are not affected by hepatic or renal impairment (5). Since it is a drug that can be well tolerated by the body, the side
effects seen are usually minor such as eczema and flatulence. In the present study, no serious side effects were observed after treatment.

There were some limitations to this study, primarily that it was designed retrospectively and the results were drawn from patient records. In addition, there were no data available of bone turnover markers and bone fracture history evaluated in patient follow-ups other than BMD. However, the high number of patients and the fact that only patients using regular medication were included in the study can be considered strong aspects of the study.

**Conclusion**

In the treatment of postmenopausal osteoporosis, 60 mg subcutaneous denosumab every 6 months is an effective treatment method. Those who used denosumab for two years had better BMD improvements than those who used it for one year. In addition, lumbar BMD improvements were better in the group that did not use regular oral bisphosphonates before treatment. To the best of our knowledge, present study is the denosumab study conducted in the largest patient population in Turkey. Further randomized controlled studies are required to determine the long-term effects and side-effects of the drug, the effect of prior use of bisphosphonates on the treatment, and the effect on clinical symptoms other than bone density.

**References**


This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Aras B, Kuzu Ö. The effectiveness of denosumab in the treatment of postmenopausal osteoporosis. Erciyes Med J 2021; DOI: 10.14744/etd.2021.79803.

©Copyright 2021 by Erciyes University Faculty of Medicine - Available online at: www.erciyesmedj.com


Figure Legend:

Figure-1 Flow chart of the study

Table Legend:

Table-1 Bone Mineral Density and T-score values before and after Denosumab treatment

Table-2 Comparison of changes in Bone Mineral Density and T-scores between groups had used regular oral bisphosphonate before denosumab treatment and who had not used regular oral bisphosphonate before denosumab treatment
Table-3 Comparison of changes in BMD and T-scores in patients using denosumab treatment for one year and two years.

Table-1 Bone Mineral Density and T-score values before and after Denosumab

<table>
<thead>
<tr>
<th></th>
<th>One year treatment (n=88)</th>
<th>Two years treatment (n=28)</th>
<th>Total (n=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Aras B, Kuzu Ö. The effectiveness of denosumab in the treatment of postmenopausal osteoporosis. Erciyes Med J 2021; DOI: 10.14744/etd.2021.79803.

©Copyright 2021 by Erciyes University Faculty of Medicine - Available online at: www.erciyesmedj.com
<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment Median (Q1-Q3)</th>
<th>Post-treatment Median (Q1-Q3)</th>
<th>P</th>
<th>Pre-treatment Median (Q1-Q3)</th>
<th>Post-treatment Median (Q1-Q3)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total femur BMD</td>
<td>0.813 (0.726-0.865)</td>
<td>0.819 (0.740-0.884)</td>
<td>&lt;0.0</td>
<td>0.803±(0.789-0.943)</td>
<td>0.839(0.789-0.943)</td>
<td>&lt;0.0</td>
</tr>
<tr>
<td>Total femur T-score</td>
<td>-1.550 (-1.200-2.100)</td>
<td>-1.500 (-1.100-2.000)</td>
<td>&lt;0.0</td>
<td>-1.650(-1.200-2.170)</td>
<td>-1.500(-1.100-2.100)</td>
<td>&lt;0.0</td>
</tr>
<tr>
<td>Femur neck BMD</td>
<td>0.799 (0.720-0.855)</td>
<td>0.815 (0.754-0.875)</td>
<td>&lt;0.0</td>
<td>0.792 (0.727-0.858)</td>
<td>0.807 (0.748-0.869)</td>
<td>&lt;0.0</td>
</tr>
<tr>
<td>Femur neck T-score</td>
<td>-1.840 (-1.450-2.200)</td>
<td>-1.745 (-1.420-2.150)</td>
<td>&lt;0.0</td>
<td>-1.877(-1.450-2.200)</td>
<td>-1.770±0.7 (-1.370-2.200)</td>
<td>&lt;0.0</td>
</tr>
<tr>
<td>Total vertebra BMD</td>
<td>0.676 (0.630-0.724)</td>
<td>0.721 (0.680-0.761)</td>
<td>&lt;0.0</td>
<td>0.694±(0.674-0.740)</td>
<td>0.740(0.66-0.790)</td>
<td>&lt;0.0</td>
</tr>
<tr>
<td>Total vertebra T-score</td>
<td>-3.300(-3.000-3.700)</td>
<td>-3.000(-3.000-3.350)</td>
<td>&lt;0.0</td>
<td>-3.200(-2.850-3.270)</td>
<td>-2.850(-2.600-3.270)</td>
<td>&lt;0.0</td>
</tr>
</tbody>
</table>

BMD: Bone mineral density, p<0.05, IQR: Interquartile Range
Table 2: Comparison of changes in Bone Mineral Density and t scores between groups who had used regular oral bisphosphonate before denosumab treatment and who had not used regular oral bisphosphonate before denosumab treatment

<table>
<thead>
<tr>
<th></th>
<th>Had used OB (n=88)</th>
<th>Had not used OB (n=28)</th>
<th>Changes</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-treatment</td>
<td>Post-treatment</td>
<td>Changes</td>
<td>Pre-treatment</td>
</tr>
<tr>
<td></td>
<td>Median (Q1-Q3)</td>
<td>Median (Q1-Q3)</td>
<td>Median (Q1-Q3)</td>
<td>Median (Q1-Q3)</td>
</tr>
<tr>
<td>Total femur BMD</td>
<td>0.813(0.72)</td>
<td>0.823(0.75)</td>
<td>0.023</td>
<td>0.790(0.7)</td>
</tr>
<tr>
<td>Total femur T-score</td>
<td>-1.600(-1.200)</td>
<td>-1.550(1.2175)</td>
<td>0.100</td>
<td>-1.600(-0.950)</td>
</tr>
<tr>
<td>Femur neck BMD</td>
<td>0.811(0.736-0.868)</td>
<td>0.811(0.875)</td>
<td>0.021</td>
<td>0.782(0.702)</td>
</tr>
<tr>
<td>Femur neck T-score</td>
<td>-1.750(-1.350)</td>
<td>-1.700(2.200)</td>
<td>0.100</td>
<td>-1.750(-1.150)</td>
</tr>
<tr>
<td>Total vertebra BMD</td>
<td>0.969(0.62-0.725)</td>
<td>0.725(0.67-0.875)</td>
<td>0.029</td>
<td>0.671(0.6-0.725)</td>
</tr>
<tr>
<td>Total vertebra T-score</td>
<td>-3.200(-2.700)</td>
<td>-3.200(-2.900)</td>
<td>0.200</td>
<td>-3.400(-2.700)</td>
</tr>
</tbody>
</table>

BMD: Bone mineral density, OB: oral bisphosphonate, QR: Interquartile Range p<0.05

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Aras B, Kuzu Ö. The effectiveness of denosumab in the treatment of postmenopausal osteoporosis. Erciyes Med J 2021; DOI: 10.14744/etd.2021.79803.

©Copyright 2021 by Erciyes University Faculty of Medicine - Available online at: www.erciyesmedj.com
Table-3 Comparison of changes in BMD and t scores in patients using denosumab treatment for one year and two years.

<table>
<thead>
<tr>
<th></th>
<th>One year treatment (n=88) Median (Q1-Q3)</th>
<th>Two years treatment (n=28) Median (Q1-Q3)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total femur BMD</td>
<td>0.014 (-0.010 0.040)</td>
<td>0.035 (0.021 0.073)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total femur T-Score</td>
<td>0.100 (-0.300 0.100)</td>
<td>0.150 (0.500 0.100)</td>
<td>0.001</td>
</tr>
<tr>
<td>Femur neck BMD</td>
<td>0.011 (-0.020 0.040)</td>
<td>0.032 (0.021 0.069)</td>
<td>0.001</td>
</tr>
<tr>
<td>Femur neck T-Score</td>
<td>0.100 (-0.300 0.100)</td>
<td>0.250 (0.500 0.100)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total vertebra BMD</td>
<td>0.034(0.013 0.052)</td>
<td>0.034 (0.017 0.054)</td>
<td>0.678</td>
</tr>
<tr>
<td>Total vertebra T-Score</td>
<td>0.300 (0.450 0.100)</td>
<td>0.250(0.400 0.100)</td>
<td>0.825</td>
</tr>
</tbody>
</table>

BMD: Bone mineral density, p<0.05