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ORIGINAL ARTICLE – OPEN ACCESS

The Effectiveness of Denosumab in the Treatment of Postmenopausal Osteoporosis

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ABSTRACT

Objective: The purpose of this study was to examine the effectiveness of denosumab to treat postmenopausal osteoporosis, and the impact of prior osteoporosis drug use and the duration of denosumab use on the success of the treatment.

Materials and Methods: In all, 116 patients who had been diagnosed with postmenopausal osteoporosis and were treated with denosumab were enrolled in the study. The primary study groups were those who had used oral bisphosphonates before denosumab treatment (n=88) and those who had not (n=28). The outcome measures were the L1-L4 lumbar vertebra, total femur, and femoral neck T-scores, and bone mineral density (BMD) values. All of the patients were evaluated pre-treatment and again at 1 and 2 years after denosumab treatment.

Results: Significant improvements were seen in the total vertebral BMD and T-scores, total femur, and femoral neck BMD and T-scores in both patient groups 1 year after treatment. The total lumbar vertebra BMD and T-scores were statistically significantly higher in the group that had not used oral bisphosphonates compared with those of the group that had used oral bisphosphonates. The total femur and femoral neck BMD and T-scores were also significantly higher after 2 years of use of denosumab in comparison with the results at 1 year of use.

Conclusion: The results indicated that denosumab is an effective treatment for postmenopausal osteoporosis; however, additional randomized controlled studies are needed to further examine the effectiveness of long-term denosumab treatment and prior bisphosphonate use.

Keywords: Denosumab, oral bisphosphonates, osteoporosis, postmenopausal

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INTRODUCTION

Osteoporosis is a systemic skeletal disease characterized by bone fragility as a result of decreased bone mass and deterioration of the micro-architectural structure of bone tissue (1). Postmenopausal osteoporosis is common, as the reduced estrogen level leads to more bone resorption than bone formation. Consequently, fractures can occur as a result of spontaneous or low-energy trauma due to deterioration of the bone quality. The most common fracture locations are the vertebrae, the proximal hip, and the wrist. (2). Some patients who sustain an osteoporotic hip fracture do not regain their pre-fracture functional capacity. Osteoporosis and subsequent fractures are a significant source of morbidity and mortality (3). In addition to the fracture risk, osteoporosis also has a negative effect on quality of life due to pain and reduced physical function (4).

Several drugs that inhibit bone resorption and stimulate bone formation are used to treat osteoporosis (2). Bisphosphonates, which reduce bone resorption by inhibiting osteoclast cells, are widely used as first-line treatment for osteoporosis. Denosumab, another therapeutic agent that inhibits bone resorption, is a human-derived monoclonal antibody directed against receptor activity 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 receptor and disrupts the function and formation of osteoclasts, resulting in reduced bone loss (5). The United States Food and Drug Administration has approved use of the drug for the treatment of postmenopausal osteoporosis with a high risk of fracture. In studies of patients with postmenopausal osteoporosis, it has been reported that the rate of hip fractures as well as vertebral and non-vertebral fractures decreased with denosumab treatment (6). A meta-analysis that compared the effect of denosumab and oral bisphosphonates in postmenopausal osteoporosis revealed that the bone mineral density (BMD) of the lumbar spine, total hip, femoral neck, and 1/3 radius was significantly greater in the denosumab group (7).

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

MATERIALS and METHODS

Ethics Approval

The study protocol was approved by the clinical research ethics committee of Kastamonu Training and Research Hospital on January 28, 2021 (KAEK no: 143-25). The research was conducted in accordance with the principles of the Helsinki Declaration.

Study Design and Participants

The medical records of patients treated for postmenopausal osteoporosis between January 2018 and January 2021 were reviewed retrospectively. The patients included in the study were those treated with 60 mg subcutaneous denosumab for 6 months with low total femur/femoral neck and/or lumbar vertebra BMD values (≤–2.5 SD) and had annual BMD follow-up examinations. Patients who did not have regular denosumab injections or without records of an annual BMD examination were excluded. Clinical osteoporosis risk factors (age, gender, smoking, alcohol use, low body mass index, family history of fracture, secondary osteoporosis causes) of the study group were also evaluated. Patients with a type of osteoporosis other than postmenopausal osteoporosis (premenopausal, senile, juvenile) and patients with causes of secondary osteoporosis (hypothyroidism, gastrointestinal disorders, rheumatological or hematological disorders, chronic renal or hepatic disease, alcoholism, metabolic bone disease, use of a drug that could influence bone metabolism) were also excluded from the study. Demographic and clinical data, and details of the duration of denosumab use, history of osteoporosis drug use before denosumab, and unresponsiveness or intolerance to oral bisphosphonates were recorded.

The BMD of all of the patients was measured using dual X-ray absorptiometry (Stratos dRş DMS Imaging, Gallargues-le-Montueux, France), at the beginning and at the end of the 12th- and 24th-month follow-up. The L1-L4 lumbar vertebrae and total femur and femoral neck BMD values and T-scores were recorded. A T-score of ≤–2.5 SD was defined as osteoporosis.

Although denosumab is a frequently used drug in the treatment of postmenopausal osteoporosis in Turkey, there are some requirements to receive reimbursement from national healthcare funding. Patients must be either unable to tolerate oral bisphosphonates or be unresponsive to oral bisphosphonate therapy before initiating the use of denosumab. Therefore, the patients included in this study were also segregated into 1 group that had been unresponsive to oral bisphosphonate treatment for at least 1 year, and another group that had not been able to tolerate oral bisphosphonates for gastrointestinal reasons after the first dose.

The patients were further grouped according to how many years they had been treated: patients with data for only 1 year (12 months) and patients with data for 2 years (24 months). BMD and T-scores at 0 and 12 months for patients with 1-year data and at 0 and 24 months for patients with 2-year data were analyzed.

Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics for Macbook, Version 20.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were displayed as mean±SD values for continuous variables and as number and frequency for categorical variables. Normal distribution of the 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 in the parameters were evaluated with the Mann-Whitney U test. A p value of <0.05 represented statistical significance.

RESULTS

The records of 152 patients who received denosumab treatment for a diagnosis of postmenopausal osteoporosis were evaluated. A total of 36 patients were not eligible for the study: 21 patients were eliminated due to a lack of annual BMD records and 15 patients due to secondary osteoporosis. A 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/m^2. The history revealed that 28 patients (24.1%) were prescribed denosumab because they could not tolerate oral bisphosphonates, and in the unresponsive

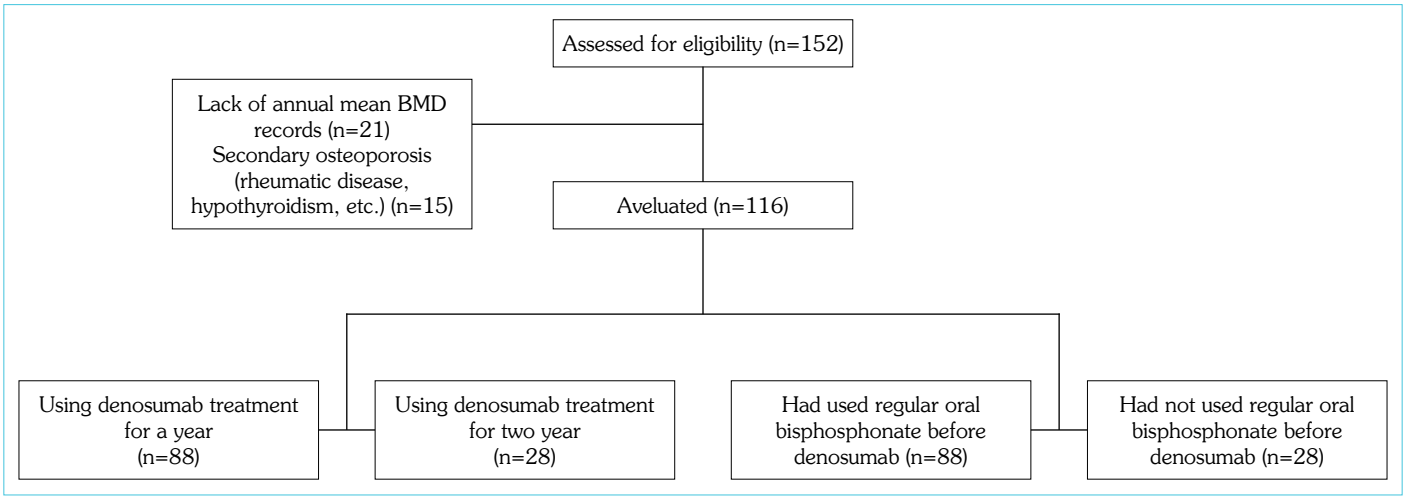

Figure 1. Flow chart of the study

BMD: Bone mineral density

group, there were 42 patients (36.2%) who had previously used alendronate, and 46 (39.7%) who 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 2-year results for 28 (24.1%).

Overall, after treatment, improvement was observed in 84 (72.4%) total femur and femoral neck BMD scores and in 101 (87.0%) total lumbar vertebra BMD scores. Statistically significant improvements were observed in the post-treatment total vertebral BMD and T-scores, and total femur and femoral neck BMD and T-scores when compared with initial values (Table 1).

When the patients were grouped according to oral bisphosphonate use before denosumab treatment, it was observed that the total lumbar vertebrae T-scores and BMD measurements were statistically significantly greater in the group that did not previously use oral bisphosphonates compared with the group that did. No significant difference was determined between the groups with respect to the total femur and femoral neck BMD values or T-scores (Table 2).

When the patients were grouped according to the duration of denosumab use, the change in total femur and femoral neck BMD values and T-scores in the group that had used denosumab for 2 years was significantly greater than that of the 1-year group. No significant difference was determined between these groups in the changes in total lumbar spine BMD values or T-scores (Table 3).

No serious side effects were observed as a result of denosumab treatment.

DISCUSSION

This study was a 3-year analysis of the results of patients of a rehabilitation hospital who used denosumab for postmenopausal osteoporosis. Positive improvements were observed in lumbar and femur BMD and T-scores after the use of 60 mg denosumab injections every 6 months. When the patients were grouped according to the duration of treatment, the improvement in the total femur and femoral neck BMD and T-scores of the patients using denosumab for 2 years was significant. When the patients were grouped according to previous oral bisphosphonate use, the lumbar BMD and T-scores were more significant in the group that had not previously used oral bisphosphonates.

In the 3-year, phase III 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, the rapid decrease in bone turnover markers observed immediately after the subcutaneous administration of 60 mg denosumab began to increase 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). It has also been noted that iliac bone biopsies of patients using denosumab revealed no adverse effects on bone mineralization, lamellar bone formation, or bone microarchitecture, however

Table 1. Bone mineral density and T-score values before and after denosumab

	One year of treatment (n=88)			Two years of treatment (n=28)			Total (n=116)		
	Pre-treatment Median (Q1-Q3)	Post-treatment Median (Q1-Q3)	p	Pre-treatment Median (Q1-Q3)	Post-treatment Median (Q1-Q3)	p	Pre-treatment Median (Q1-Q3)	Post-treatment Median (Q1-Q3)	p
Total femur BMD	0.813 (0.726–0.865)	0.819 (0.740–0.884)	**<0.001**	0.803±(0.727–0.873)	0.839 (0.789–0.943)	**<0.001**	0.811 (0.727–0.865)	0.823 (0.762–0.888)	**<0.001**
Total femur T-score	–1.550 (–1.200–2.100)	–1.500 (–1.100–2.000)	**<0.001**	–1.650 (–1.200–2.170)	–1.500 (–0.750–1.700)	**<0.001**	–1.600 (–1.200–2.100)	–1.520 (–1.100–1.970	**<0.001**
Femoral neck BMD	0.799 (0.720–0.855)	0.815 (0.754–0.875)	**<0.001**	0.792 (0.727–0.858)	0.807 (0.748–0.869)	**<0.001**	0.797 (0.756–0.888)	0.813 (0.753–0.876)	**<0.001**
Femoral neck T-score	–1.840 (–1.450–2.200)	–1.745 (–1.420–2.150)	**<0.001**	–1.877 (–1.450–2.200)	–1.770±0.730 (–1.370–2.100)	**<0.001**	–1.850 (–1.420–2.200)	–1.760 (–1.330–2.100)	**<0.001**
Total vertebra BMD	0.676 (0.630–0.724)	0.721 (0.680–0.761)	**<0.001**	0.694 (0.630–0.741)	0.740 (0.668–0.790)	**<0.001**	0.690 (0.630–0.734)	0.725 (0.679–0.766)	**<0.001**
Total vertebra T-score	–3.300 (–2.970–3.700)	–3.000 (–2.700–3.350)	**<0.001**	–3.200 (–2.800–3.700)	–2.850 (–2.600–3.270)	**<0.001**	–3.250 (–2.900–3.700)	–2.900 (–2.600–3.300)	**<0.001**

p<0.05. BMD: Bone mineral density; IQR: Interquartile range

Table 2. Comparison of changes in bone mineral density and T-scores between groups that had and had not used an oral bisphosphonate before denosumab treatment

	Had used OB (n=88)			Had not used OB (n=28)			p
	Pre-treatment Median (Q1-Q3)	Post-treatment Median (Q1-Q3)	Change Median (Q1-Q3)	Pre-treatment Median (Q1-Q3)	Post-treatment Median (Q1-Q3)	Change Median (Q1-Q3)	
Total femur BMD	0.813 (0.726–0.865)	0.823 (0.751–0.884)	0.023 (0.005–0.041)	0.790 (0.732–0.889)	0.829 (0.772–0.890)	0.020 (0.005–0.058)	0.268
Total femur T-score	–1.600 (–1.200–2.175)	–1.550 (–1.100–2.000)	0.100 (–0.300 0.100)	–1.600 (–0.950–2.000)	–1.550 (–1.075–1.775)	0.100 (–0.300 0.000)	0.790
Femoral neck BMD	0.801 (0.736–0.868)	0.811 (0.744–0.875)	0.021 (0.001–0.041)	0.782 (0.702–0.865)	0.804 (0.780–0.878	0.019 (0.005–0.038)	0.524
Femoral neck T-score	–1.750 (–1.350–2.200)	–1.700 (–1.200–2.100)	0.100 (–0.200 0.100)	–1.750 (–1.150–2.200)	–1.700 (–1.400–2.100)	0.100 (–0.300 0.100)	0.790
Total vertebra BMD	0.696 (0.623–0.735)	0.725 (0.670–0.767)	0.029 (0.014–0.048)	0.671 (0.641–0.884)	0.731 (0.699–0.776)	0.051 (0.030–0.070)	**0.017**
Total vertebra T-score	–3.200 (–2.900–3.800)	–2.900 (–2.600–3.400)	0.200 (–0.400–0.100)	–3.400 (–3.200–3.700)	–3.000 (–2.600–3.125)	0.400 (–0.600–0.200)	**0.020**

p<0.05. BMD: Bone mineral density; OB: Oral bisphosphonate; QR: Interquartile range

results beyond 3 years were not determined results beyond 3 years were not determined (12). In this retrospective study, patients were excluded if they had not received regular denosumab subcutaneous injections every 6 months. The study results revealed positive improvements in the BMD and T-scores of all of the patients.

European guidelines for the diagnosis and management of postmenopausal osteoporosis published in 2019 recommend oral bisphosphonates (alendronate, risedronate, ibandronate) as the first-line therapy for most patients and intravenous bisphosphonates and denosumab are recommended for patients who cannot tolerate oral bisphosphonates. Hormone replacement therapy and raloxifene are other alternative pharmacological treatment options. Teriparatide has been recommended for patients with a high fracture risk (1). Studies of combination or sequential drug use still do not provide sufficient data on fracture prevention. The most accepted view is that treatment with anabolic drugs, such as teriparatide, should be limited to 18–24 months, and because the effect decreases when the treatment is terminated, it should be followed by use of an anti-resorptive drug (bisphosphonate, denosumab, etc.) (13–14).

The literature includes some controlled studies that have compared denosumab and bisphosphonates in the treatment of postmenopausal osteoporosis. Denosumab has been shown to demonstrate more significant improvements in total hip, lumbar vertebrae, trochanter, and radius BMD scores than weekly alendronate (15, 16) and monthly ibandronate (17) and risedronate (18) treatments. In a study of patients who had previously used an oral bisphosphonate, it was reported that denosumab achieved more significant results in total vertebrae, total hip, and radius BMD scores compared with zoledronic acid (19). Another study examined minodronate, which is a third-generation bisphosphonate and considered the strongest suppressor of bone resorption among bisphosphonates, more significant improvements were found in BMD and bone turnover markers in the group that switched from minodronate to denosumab treatment when compared with the group that continued to use minodronate (20). The conclusion of a meta-analysis of 5361 patients conducted by Lyu et al. (21) that compared denosumab and bisphosphonates found that denosumab had a greater effect on the total hip, femoral neck, and total lumbar vertebrae BMD scores, but also noted that additional studies were needed to consider a number of potentially influential factors (21).

The different mechanism of action of denosumab appears to provide more significant improvement than bisphosphonates as a result of earlier bone remodeling (22). The results of the current study illustrated statistically significant improvement in the BMD data of the patients and it may therefore be an option for those unresponsive to oral bisphosphonate therapy.

It remains unclear whether the use of bisphosphonates prior to denosumab treatment has an effect on treatment. In a study conducted by Nakamura et al. (23) of patients with rheumatoid arthritis, positive effects were observed in the BMD scores of groups that had and had not used 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. Suzuki et al. (24) examined the effect of long-term use of bisphosphonates before denosumab treatment and concluded that

Table 3. Comparison of change in BMD and T-scores in patients using denosumab treatment for 1 year and 2 years

	One year of treatment (n=88) Median (Q1-Q3)	Two years of treatment (n=28) Median (Q1-Q3)	p
Total femur BMD	0.014 (–0.010 0.040)	0.035 (0.021 0.073)	**0.001**
Total femur T-Score	0.100 (–0.300 0.100)	0.150 (0.500 0.100)	**0.001**
Femoral neck BMD	0.011 (–0.020 0.040)	0.032 (0.021 0.069)	**0.001**
Femoral neck T-Score	0.100 (–0.300 0.100)	0.250 (0.500 0.100)	**0.001**
Total vertebra BMD	0.034 (0.013 0.052)	0.034 (0.017 0.054)	0.678
Total vertebra T-Score	0.300 (0.450 0.100)	0.250 (0.400 0.100)	0.825

p<0.05. BMD: Bone mineral density

the lumbar BMD scores were significantly more improved in the group that had not received bisphosphonates before denosumab. It was observed 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 improvement was observed in the lumbar spine BMD and T-scores in the group of patients who were using denosumab because they could not tolerate oral bisphosphonates when compared with the group that had used oral bisphosphonates for at least 1 year. The effect of previous use of bisphosphonates on the results of subsequent denosumab use remain uncertain, however, 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 of long-term effects of denosumab, the results indicated 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 femoral neck BMD and T-scores of the patient group that had used denosumab for 2 years (24 months) when compared with the 1-year (12 months) denosumab group.

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). It is generally well tolerated; the side effects seen are usually minor, such as skin irritations. In the present study, no serious side effects were observed after treatment.

Limitations

Limitations of this study include the retrospective design and the fact that there were no data available of evaluation of bone turnover markers or bone fracture history in patient follow-ups other than BMD. The relatively large number of patients and the fact that only patients using regular medication were included in the study can be considered a strength.

CONCLUSION

A 60-mg injection of denosumab every 6 months was demonstrated to be an effective form of treatment of postmenopausal osteoporosis. The patients who had used denosumab for 2 years had greater BMD improvement than those who had used it for 1 year, suggesting an accumulative effect. The findings also indicated that the lumbar BMD improvements were better in the group that had not used oral bisphosphonates before treatment with denosumab. To the best of our knowledge, the present study is the largest to examine denosumab use in Turkey. While the results are notable, further randomized controlled studies are required to determine the long-term effects and side effects of the drug, and further explore the effect of prior use of bisphosphonates on denosumab treatment, and the effect on clinical symptoms other than bone density.

Ethics Committee Approval: The Kastamonu Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 28.01.2021, number: KAEK-143-25).

Informed Consent: Informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – BA, ÖK; Design – BA, ÖK; Supervision – BA; Resource – BA; Materials – BA, ÖK; Data Collection and/or Processing – BA, ÖK; Analysis and/or Interpretation – BA, ÖK; Literature Search – BA, ÖK; Writing – BA, ÖK; Critical Reviews – BA, ÖK.

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