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Denosumab and Bisphosphonate Treatment of Osteoporosis in Renal Transplant Recipients

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Abstract

Objective: Kidney transplant recipients are at risk of losing bone mineral density. Osteoporosis and fractures cause serious complications in renal transplant recipients. We aimed to evaluate the efficacy and safety of bisphosphonate and denosumab treatments.

Methods: Thirty-two renal transplant patients with osteoporosis from Division of Nephrology of İstanbul University-Cerrahpaşa were retrospectively evaluated. Ten patients were treated with denosumab, 22 patients were treated with bisphosphonate. Time elapsed after transplantation, cumulative steroid doses, baseline and first-year calcium, phosphorus, parathyroid hormone, and the glomerular filtration rate were compared. The initial and first-year femur and lumbar bone mineral densities were compared for both groups separately.

Results: The baseline femur bone mineral density was significantly lower in the denosumab arm, but there was no significant difference between the initial lumbar bone mineral densities between groups. There was a significant increase in lumbar bone mineral density for both the denosumab and bisphosphonate arms in the first year of treatment. For both groups, there was no significant increase in femur bone mineral density in the first year of treatment. The time elapsed after transplantation and cumulative steroid dose were higher in the denosumab arm. Glomerular filtration rate levels of the denosumab arm were lower compared to bisphosphonate arm. Hypocalcemia associated with antiresorptive agent was not found in the treatment arms. In the first year of treatment, calcium levels were significantly lower in the denosumab treatment arm.

Conclusion: Denosumab is an effective treatment option, especially in renal transplant patients with a low glomerular filtration rate.

Keywords: Denosumab, kidney transplantation, osteoporosis, transplant recipients

Renal Transplant Alıcılarında Osteoporozun Denosumab ve Bisfosfonat Tedavisi

Öz

Amaç: Renal transplant alıcılarında kemik mineral yoğunluğunun (KMY) azalma riski vardır. Osteoporoz ve osteoporoza bağlı kırıklar ciddi komplikasyonlara neden olabilirler. Bu çalışmada denosumab ve bifosfonatın etkinliğini ve güvenilirliğini değerlendirmeyi amaçladık.

Yöntemler: İstanbul Üniversitesi-Cerrahpaşa Nefroloji Bilim Dalı'nda takipli osteoporozu olan 32 renal transplant alıcısı retrospektif olarak incelendi. Hastalardan 10'u denosumab ile 22'si bifosfonat ile tedavi alıyordu. Hastaların transplantasyondan sonraki süreleri, kümülatif steroid dozları, başlangıç ve birinci yıl kalsiyum, fosfor, paratiroid hormon ve glomerüler filtrasyon hızları (GFR) karşılaştırıldı. Başlangıç ve birinci yıl femur ve lomber KMY değerleri grup içinde ve gruplararası karşılaştırıldı.

Bulgular: Denosumab tedavi kolunda başlangıç femur KMY değerleri anlamlı olarak daha düşük saptandı, ancak lomber KMY değerleri arasında anlamlı bir fark saptanmadı. Tedavinin ilk yılında her iki tedavi kolunda lomber KMY değerlerinde anlamlı bir artış saptanırken

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femur KMY değerlerinde anlamlı bir artış olmadı. Transplantasyondan sonraki süre ve kümülatif steroid dozları denosumab tedavi kolunda anlamlı olarak daha yüksekti. Denosumab tedavi kolunda başlangıç GFR anlamlı olarak daha düşüktü. Tedavi kollarında antirezorptif ajanla ilişkili hipokalsemi saptanmadı. Tedavinin birinci yılında, denosumab tedavi kolunda kalsiyum düzeyleri anlamlı olarak daha düşük saptandı.

Sonuç: Denosumab tedavisi, özellikle düşük GFR'ye sahip renal transplant hastalarında etkili ve güvenilir bir tedavi seçeneğidir.

Anahtar Kelimeler: Denosumab, osteoporoz, renal transplantasyon, transplant alıcıları

Renal transplantation is the preferred renal replacement therapy type in end-stage renal disease.[1] In addition to the improvement in renal function after a successful transplant, anemia, secondary hyperparathyroidism, and other problems related to uremia also improve significantly. However, disorders of bone mineral metabolism seen in chronic kidney disease may persist in the post-transplant period.[2,3]

Osteoporosis is an important complication during the post-transplant period, and fractures due to untreated osteoporosis have been associated with increased morbidity and mortality.[4] The risk of osteoporosis was found to be more than 5 times greater in organ transplant patients than that of the general population, and the highest rate of bone loss is seen in the first year following transplantation. In the post-transplant period, persistent hyperparathyroidism, vitamin D deficiency, corticosteroids, and immunosuppressive agents cause lower bone mineral density (BMD) in renal transplant recipients.[5,6]

Vitamin D, calcitriol/alfacalcidol, and antiresorptive agents are recommended in the treatment of osteoporosis in renal transplant recipients. Although bisphosphonate treatment prevents bone loss in the post-transplant period, it is not suitable for patients with a low glomerular filtration rate (GFR).[7,8] Denosumab is a receptor activator nuclear kappa B ligand human monoclonal antibody developed for the treatment of osteoporosis. It inhibits osteoclast formation, decreases bone resorption, increases BMD, and reduces the risk of fracture.[9,10] There may be some side effects due to inhibition of the Receptor activator of nuclear factor-kappa-B (RANK)/Receptor activator of nuclear factor-kappa-B ligand (RANKL) pathway. For instance, urinary tract infection is one of these side effects. However, there are not enough studies on this subject. Urinary tract infection due to denosumab is probably multifactorial. It has been reported that inhibition of the RANK/RANKL pathway may reduce resistance to microbial organisms by unknown mechanisms.[11,12] But, the mechanisms underlying the urinary tract infections due to denosumab remain unclear.

There are several studies showing that denosumab is effective for the treatment of osteoporosis in renal transplant recipients,[13,14] but comparative data with bisphosphonate therapy in the same setting are largely missing. The aim of this study was to investigate the effects of denosumab and bisphosphonate treatments on osteoporosis of renal transplant recipients who were followed up in the same transplant unit.

Methods

We collected data regarding antiresorptive therapy in renal transplant recipients who were followed up in our renal transplantation unit. Patients with complete medical records were included in the study, and the groups were matched according to age and sex. The exclusion criteria for antiresorptive treatment were as follows: malignancy, age <18 years, hypoparathyroidism, and hypo- or hypercalcemia before treatment. The denosumab treatment arm consisted of 10 patients, and the bisphosphonate treatment group comprised 22 patients. Demographic, clinical, and laboratory data were collected from the medical records of the patients.

Bone mineral density and vitamin D, calcium, phosphorus, and parathormone (PTH) levels were used to evaluate the bone health of the patients. Z-scores were used for evaluation of BMD in male patients aged less than 50 years and in premenopausal women. T-scores were used for evaluation of BMD in male patients aged higher than 50 years and in postmenopausal women. The BMD values of the patients were measured using dual-energy X-ray absorptiometry (DEXA) (Hologic). Patients with a history of fragility fractures, patients with Z-scores ≤ -2 with ongoing bone loss, and patients with T-scores ≤ -2.5 were treated for osteoporosis.[15,16] The denosumab treatment decision was given according to the following criteria: patients who completed the bisphosphonate treatment period and/or had decreased creatinine clearance when receiving bisphosphonate treatment (creatinine clearance <30 mL/min/1.73 m^2). All patients were prescribed daily supplements of calcium (1000 mg) and vitamin D (800 IU or more). Selected patients were followed up for 1 year according to routine outpatient clinic follow-up measures, and a second DEXA evaluation was made at the end of the 12th month after the initial DEXA measurement. The patients were evaluated for osteoporotic fractures. Osteoporotic fragility fracture was defined as fractures occurring mainly in the vertebral column, hip, forearm, and shoulder region associated with low bone density.[17]

The initial and first-year BMD values were compared between the treatment groups. The initial and first-year BMD values were also compared within the groups. Baseline and first-year estimated GFR (e-GFR), creatinine, calcium, phosphorus, albumin, PTH, and vitamin D levels were compared within the groups and between the groups. The cumulative steroid doses, 1-year cumulative steroid doses during the study period, use of calcineurin inhibitors and mycophenolic acid, hospitalization rate, and frequency of urinary tract infections were compared between the groups. After the groups were matched according to baseline age and femur and lumbar BMD values, BMD changes after 1 year were compared. The cumulative steroid dose was calculated as the total dose taken by the patient starting from the date of transplantation and during the antiresorptive treatment, and 1-year cumulative steroid dose during the study period was calculated as the total steroid dose taken during the 1 year of antiresorptive treatment. Cumulative steroid and pulse steroid doses were calculated starting from the date of transplantation to the time of evaluation of BMD.

This study was approved by the Local Ethics Committee of Cerrahpasa School of Medicine in accordance with the Helsinki Declaration Principles (reference no: 106456). All patients read and signed informed consent forms.

Statistical analysis

The characteristics of the patients were described using descriptive statistics. Categorical data are stated as counts and proportions, and continuous data are stated as mean, standard deviation, median, and minimum–maximum. The statistical differences between the groups were calculated using the Chi-square test in nominal variables. The distribution normality of the quantitative variables was calculated using the Shapiro–Wilk test; normally distributed variables were compared between the groups using the independent-samples *t* test, and non-normally distributed variables were compared using the Mann–Whitney U test. The paired-samples *t* test or Wilcoxon signed-ranks test were used to determine any significant differences between repeated measures. Propensity score matching for age and femur and lumbar BMD values was performed to compare patients in the denosumab and bisphosphonate groups. Propensity score matching and all the other statistical analyses were performed using the IBM Statistical Package for the Social Sciences (IBM SPSS Corp., Armonk, NY, USA) v.24 for Windows software and the NCSS statistical software. Values of $P < .05$ were considered significant.

Results

The general characteristics and initial laboratory values of both groups are shown in Table 1. The mean age of the patients in the denosumab treatment arm was 52.35 ± 13.42 years, and there are 3 male and 7 female patients. The mean age of the patients receiving bisphosphonate was 46.6 ± 12.9 years, and there are 33 male and 9 female patients. While 7 patients were using ibandronate (150 mg/month), 15 patients were using alendronate (70 mg/week). Denosumab was used as 60 mg/6 months. In the denosumab treatment arm, half of the patients undergoing kidney transplantation received a cadaveric organ, and the other half received organs from a living kidney donor. In the bisphosphonate treatment arm, 7 patients received a cadaveric organ and 15 patients had living kidney donor organs. General features of the patients matched according to age and baseline femur and lumbar BMD values are presented in Table 2.

There was a significant difference between groups in terms of basal e-GFR values ($P = .025$). But after 1 year of treatment, there was no significant difference in e-GFR between the groups. In addition, we did not detect significant e-GFR change after 1-year in the denosumab and bisphosphonate treatment arms. No fractures were seen in either group before and during the 1-year treatment period. Eight patients (80%) were using calcineurin inhibitors and 7 patients (70%) were using mycophenolic acid in the denosumab treatment arm. In the bisphosphonate treatment arm, 22 patients were using calcineurin inhibitors (100%) and 19 (86%) were using mycophenolic acid. None of the patients received mammalian target of rapamycin (mTOR) inhibitor therapy. There was no significant difference between the 2 groups in terms of calcineurin inhibitor and mycophenolic acid use. The cumulative steroid doses were significantly higher in the denosumab treatment arm ($P = .028$). But, there was no significant difference in terms of 1-year cumulative steroid doses during the study period ($P > .05$). Time elapsed after transplantation was significantly higher in the denosumab treatment arm ($P = .009$). There was no significant increase in urinary tract infection and hospitalization rates in either treatment group. We did not detect any antiresorptive

Table 1. General Features of Patients

	Denosumab (n = 10)	Bisphosphonate (n = 22)	*P*
Sex			
Male	3	13	.253
Female	7	9	
Transplantation type			
Living donor	5	15	.438
Cadaveric donor	5	7	
Time elapsed after transplantation (mean ± SD) (month)	151 ± 92.16	62.59 ± 60.77	**.009**
Age (mean ± SD) (year)	52.35 ± 13.42	46.66 ± 12.99	.238
Initial e-GFR (mean ± SD) (mL/min/1.73 m^2)	52.90 ± 26.01	73.50 ± 19.76	**.025**
Initial calcium (mean ± SD) (mg/dL)	9.45 ± 0.61	9.72 ± 0.55	.238
Initial phosphorus (mean ± SD) (mg/dL)	3.33 ± 0.77	3.22 ± 0.65	.476
Initial PTH median (min/max) (pg/mL)	85.70 (21.87/279.80)	106.80 (46.10/264.50)	.739
Cumulative steroid dose (mean ± SD) (g)	21.91 ± 11.62	12.27 ± 8.80	**.028**

e-GFR, estimated GFR; GFR, glomerular filtration rate; PTH, parathormone; SD, standard deviation. Statistically significant with $P < .05$.

Table 2. General Features of the Groups Matched for Age and Baseline Femur and Lumbar BMD Values

	Denosumab (n = 10)	Bisphosphonate (n = 10)	*P*
Sex			
Male	3	3	1.000
Female	7	7	
Transplantation type			
Living donor	5	6	.653
Cadaveric donor	5	4	
Time elapsed after transplantation (mean ± SD) (month)	151 ± 92.16	60.10 ± 60.75	**.015**
Age (mean ± SD) (year)	52.35 ± 13.42	49.48 ± 14.07	.579
Initial e-GFR (mean ± SD) (mL/min/1.73 m^2)	52.90 ± 26.01	69.00 ± 23.01	.143
Initial calcium (mean ± SD) (mg/dL)	9.45 ± 0.61	9.57 ± 0.56	.579
Initial phosphorus (mean ± SD) (mg/dL)	3.33 ± 0.77	3.42 ± 0.50	.796
Initial PTH median (min/max) (pg/mL)	85.70 (21.87/279.80)	90.64 (46.10/204.90)	1.000
Cumulative steroid dose (mean ± SD) (g)	21.91 ± 11.62	11.75 ± 8.38	.052

e-GFR, estimated GFR; GFR, glomerular filtration rate; PTH, parathormone; SD: standard deviation. Statistically significant with $P < .05$.

agent-related hypocalcemia in treatment arms. We did not find significant difference in terms of initial calcium between groups, but after 1 year, calcium level was significantly lower in the denosumab treatment arm compared to the bisphosphonate treatment arm ($P = .042$). On the other hand, we did not find a significant increase in terms of PTH, e-GFR, calcium, vitamin D, albumin, and phosphorus in denosumab and bisphosphonate treatment arms.

The initial femur BMD of the denosumab treatment arm was significantly lower compared to bisphosphonate treatment arm ($P = .043$); however, there was no significant difference in lumbar BMD. In the first year of treatment, no significant difference was observed between the 2 groups in terms of femur and lumbar BMDs (Table 3). There was a significant increase in the lumbar region after 1 year of treatment in the denosumab (3%) and bisphosphonate treatment (11%) arms, but the increase in femur BMDs was not statistically significant in both groups (8% vs. 5%) (Table 4).

When delta BMD in the 1-year period was compared between the groups, the increase in the lumbar region of the bisphosphonate treatment arm was significantly higher ($P = .044$), whereas there was no significant difference between the groups for the femur region ($P = .882$) (Table 5). After matching patients according to baseline age and femur and lumbar BMD values between the 2 groups, 1-year changes of BMD were compared, and there was no significant difference in either the lumbar or femur regions (Table 5).

Discussion

In this retrospective study, we analyzed the results of denosumab and bisphosphonate therapy in renal transplant patients with osteoporosis. We found that BMDs increased in the lumbar region of patients in both the denosumab and bisphosphonate therapy arms, but there was no significant increase in the femur region in the first year of treatment. In our study, the BMD change of the lumbar region was significantly higher in the bisphosphonate therapy arm, but there was no significant increase in the femur region. No difference was detected in change of the lumbar and femur region after the groups were matched. The time elapsed after transplantation and cumulative steroid doses were significantly higher in the denosumab treatment arm.

In a meta-analysis of 17 randomized controlled studies by Kan et al[18] bisphosphonate therapy was found

Table 3. Initial and Post-treatment BMD Values (Inter-group)

	Denosumab (n = 10)	Bisphosphonate (n = 22)	*P*
Initial lumbar BMD (mean ± SD) (g/cm^2)	0.77 ± 0.12	0.71 ± 0.13	.193
Initial femur BMD (mean ± SD) (g/cm^2)	0.58 ± 0.09	0.68 ± 0.13	**.043**
Post-treatment lumbar BMD (mean ± SD) (g/cm^2)	0.80 ± 0.11	0.79 ± 0.13	.051
Post-treatment femur BMD median (min/max) (g/cm^2)	0.62 (0.51/0.77)	0.69 (0.61/1.02)	.855

BMD, bone mineral density; SD, standard deviation. Statistically significant with $P < .05$.

Table 4. Initial and Post-treatment BMD Values (Intra-group)

	Initial (g/cm^2)	Post-treatment (g/cm^2)	*P*
Denosumab (mean ± SD)			
Lumbar BMD	0.77 ± 0.12	0.80 ± 0.11	**.041**
Femur BMD	0.58 ± 0.09	0.63 ± 0.09	.059
Bisphosphonate (mean ± SD)			
Lumbar BMD	0.71 ± 0.13	0.79 ± 0.13	**.002**
Femur BMD	0.68 ± 0.13	0.72 ± 0.10	.106

BMD, bone mineral density, SD, standard deviation. Statistically significant with $P < .05$.

to improve absolute change of lumbar region BMD after renal transplantation, but no significant improvement was detected in the absolute change of the femur neck BMD. But at the end of the study, there was no significant difference in femur and lumbar BMD of the bisphosphonate treatment arms compared to the control groups. A meta-analysis performed by Yang et al[19] showed that addition of bisphosphonate treatment improved BMD of lumbar and femoral region. In line with these studies, in our study, we detected significant improvement in lumbar BMD in the bisphosphonate treatment arm.

In a study conducted by Bonani et al[14] denosumab was shown to increase BMD both in the femur and lumbar region in renal transplant recipients. They found a 2.3% increase in femur BMD and a 4.6% increase in lumbar BMD. Likewise, Brunova et al[20] detected an 8% increase in femur BMD and a 10% increase in lumbar BMD. Brown et al[21] reported that denosumab was more effective than alendronate for BMD improvement at all measured skeletal sites in postmenopausal women. Suzuki et al[22] detected that denosumab significantly improved lumbar and femur BMD in patients who had not previously received bisphosphonate treatment compared with patients who previously had bisphosphonate treatment in glucocorticoid-induced osteoporosis. In our study, we detected an 8% increase in femur BMD and a 3% increase in lumbar BMD in denosumab treatment arm. In the denosumab treatment arm, there was a significant increase in lumbar region BMD, but there was no significant increase in the femur region. The increase in lumbar region BMD was found to be higher in the bisphosphonate treatment arm, but there was no increase in the femur region. The following factors should be taken into account when interpreting our results. First, cumulative steroid doses and time elapsed after transplantation were higher in the denosumab treatment arm compared to the bisphosphonate treatment arm. On the other hand, 1-year cumulative steroid doses during the study period were similar between groups during treatment period. Second, in our study, patients in the denosumab treatment arm had previously received bisphosphonate treatment. These factors might have caused blunted efficacy of denosumab in our patients. In addition, denosumab had a better effect on the lumbar region in younger male patients, in patients who had higher GFRs, and in those who had lower PTH levels.[14] In our study, e-GFR was significantly lower in denosumab treatment arm compared to the bisphosphonate treatment arm. Although not statistically significant, age and PTH level were lower in denosumab treatment arm compared to the bisphosphonate treatment arm.

Due to the retrospective and non-randomized design of our study, baseline e-GFR, cumulative steroid dose, time elapsed after transplantation, and initial femur BMD were different between groups. To address this issue, groups were matched according to baseline age and femur and lumbar BMD values using propensity analysis. After propensity score matching, delta change of lumbar BMD was found to be similar between groups.

In our study, no fractures were seen in either the denosumab or bisphosphonate treatment arms before and during the 1-year treatment period. The small number of cases and short follow-up duration might have limited the ability of this study to show a statistically significant increase in fracture risk. On the other hand, in the literature, the association between reduced fracture risk and antiresorptive therapy is controversial in renal transplant recipients. Palmer et al[23] detected that intervention for low BMD decreased the relative risk of fracture following 6-12 months of treatment in renal transplant recipients. On the other hand, the network meta-analysis conducted by Yang et al[18] reported that although new generation bisphosphonates improved BMD, the risk of fracture was not reduced by bisphosphonate treatment regimens. Denosumab reduces the risk of vertebral, nonvertebral, and hip fractures in postmenopausal women.[24] In the

Table 5. Change of BMD

	Denosumab (n = 10)	Bisphosphonate (n = 22)	*P*
Delta lumbar BMD (mean ± SD) (g/cm^2)	0.029 ± 0.034	0.079 ± 0.089	**.044**
Delta femur BMD (mean ± SD) (g/cm^2)	0.050 ± 0.073	0.046 ± 0.126	.882
Change of BMD according to the type of treatment after propensity score matching			
Delta lumbar BMD (mean ± SD) (g/cm^2)	0.029 ± 0.034	0.083 ± 0.083	.054
Delta femur BMD (mean ± SD) (g/cm^2)	0.050 ± 0.073	0.063 ± 0.107	.496

BMD, bone mineral density; SD, standard deviation. Statistically significant with $P < .05$.

literature, there are insufficient data regarding the association between decreased fracture risk and denosumab treatment in osteoporosis of renal transplantion patients. In addition, recent evidence showed that denosumab treatment had no benefit for reducing the risk of fracture when compared with bisphosphonate treatment.[25]

Bonani et al[14] found that urinary tract infections were more common in patients receiving denosumab treatment than in the control group. In our study, the frequency of urinary tract infections and hospitalization rates were not increased in patients using denosumab. However, the number of patients was small, and there was no control group without treatment. The incidence of denosumab-related hypocalcemia was 1.7% in renal transplant recipients.[26] In our study, there was no denosumab-related hypocalcemia. This condition may be related to adequate calcium and vitamin D replacement. On the other hand, although no significant difference was found in initial calcium, calcium was significantly lower in the denosumab treatment arm after 1 year of treatment. Previous studies showed that there was a significant increase in PTH level in the denosumab treatment, especially in the first year of treatment.[27,28] This increase may be related to the strong inhibition of bone resorption.[26] Nakamura et al[27] reported that denomusab treatment did not lead to an increase in PTH level in the patients receiving bisphosphonate pre-treatment, whereas there was a significant increase in PTH level in patients receiving denosumab alone. On the other hand, in the study performed by Bonani et al[14] PTH levels did not increase significantly in renal transplant recipients in the first year of the denosumab treatment. Our results were compatible with the previous 2 studies. PTH levels did not significantly increase in the denosumab treatment arm at the end of 1 year. In addition, patients in the denosumab treatment arm had previously received bisphosphonate treatment which might have limited the increase in PTH levels.

Study limitations

There are some limitations to our study. First, the number of patients was small. Second, the patients who received denosumab treatment had previously received bisphosphonate treatment. This could have biased our results. Although no fracture was seen during the study period, none of the patients were evaluated with vertebral imaging for the diagnosis of asymptomatic vertebral fractures.

Denosumab is as effective and safe as bisphosphonate treatment in renal transplant recipients with osteoporosis. Denosumab can be used as an alternative to bisphosphonates, especially in patients with low GFR and when bisphosphonate therapy is not suitable. Further prospective randomized studies with higher number of patients are necessary to better evaluate the effect of denosumab treatment in patients with renal transplantation.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University-Cerrahpaşa (Date: November 16, 2018, Number: 83088843-604.01.01-94080).

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