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Evaluation of Denosumab Efficacy after Bisphosphonate Use in Patients with Osteoporosis: A Single Center Experience

Osteoporozlu Hastalarda Bisfosfonat Kullanımı Sonrası Denosumab Etkinliğinin Değerlendirilmesi: Tek Merkez Deneyimi

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ÖZET

Amaç: Osteoporoz kemiklerdeki mineral yoğunluğunun azalması sonucu kemik kütle ve yapısının zayıflayarak kemiklerin kırılgan hale geldiği bir hastalıktır. Tedavide amaç kemik kırıklarının engellenmesidir. Osteoporoz tedavisinde yeterli kalsiyum ve D vitamini kullanılmasının yanı sıra kemik rezorbsiyonunu önleyici ve kemik yapımını arttırıcı ilaçlar kullanılmaktadır. Düşme riskini azaltıcı yaşam tarzı önlemlerinin alınması da gereklidir. Bu çalışmada osteoporozu olan Türk popülasyonunda bisfosfonat kullanımı sonrası denosumabın etkinlik ve güvenilirliğinin değerlendirilmesi amaçlandı.

Gereçler ve Yöntem: 2018-2022 yılları arasında osteoporoz tanısı alan ve denosumab kullanan hastalar çalışmaya dahil edildi. Hastaların demografik, klinik, kemik mineral yoğunluğu ve tedavi özellikleri kaydedildi. Hastaların denosumab kullanımından sonraki kemik mineral yoğunluğu değerleri tedavi öncesi başlangıç değerleri ile karşılaştırıldı.

Bulgular: Çalışmanın analizi 55 hastanın verileri ile yapıldı. Çalışmaya alınan hastaların tümü kadın olup ortanca yaş 69 (46-90)'du. Osteoporozun en sık nedeni postmenopozal (%56,4) iken, sekonder nedenler arasında en sık görülen neden ise primer hiperparatiroidizm (%14,5) idi. On dört (%25,5) hastada kırık öyküsü mevcuttu. Denosumab tedavisi sonrası hastaların fosfor (p=0,022) ve alkalen fosfataz (p<0,001) düzeylerinde istatistiksel olarak anlamlı düşüş saptandı. Denosumab tedavisi ile L1-L4 (0,887'den 0,933'e), femur boynu (0,693'ten 0,727'ye) ve total kalça (0,762'den 0,782'ye) bölgelerinde BMD (gr/cm^2) değerlerinde iyileşme gözlendi. Benzer şekilde, hastaların BMD Z skorları ve T skorlarında da iyileşme saptandı. Ayrıca denosumab ile ilişkili advers olay gözlenmedi.

Sonuç: Bu çalışmada osteoporozlu hastaların tedavi özellikleri geriye dönük olarak incelendi. Hastalarda denosumab tedavisi iyi tolere edildi ve tedavi ile ilişkili ciddi bir yan etki saptanmadı. Bisfosfonat kullanımından sonra denosumabın osteoporoz tedavisinde etkili ve güvenli bir tedavi seçeneği olduğu görüldü.

Anahtar Kelimeler: Osteoporoz, bisfosfonat, denosumab

ABSTRACT

Objective: Osteoporosis is a disease in which the bone mass and structure are weakened as a result of the decrease in the mineral density in the bones, and the bones become brittle. In addition to the use of adequate calcium and vitamin D in the treatment of osteoporosis, drugs that prevent bone resorption and increase bone formation are used. The aim of this study was to evaluate the efficacy and safety of denosumab after the use of bisphosphonates in the Turkish population with osteoporosis.

Materials and Methods: Patients diagnosed with osteoporosis and using denosumab between 2018-2022 were involved in the study. Demographic, clinical, bone mineral density, and treatment characteristics of the patients were recorded. The patient's bone mineral density values after denosumab were compared with the baseline values.

Results: Analysis of the study was performed with data from 55 patients. All patients involved in the study were female, and the median age was 69 (46-90). The most common cause of osteoporosis was postmenopausal (56.4%), and the most common cause among secondary causes was primary hyperparathyroidism (14.5%). Fourteen (25.5%) patients had a history of fracture. After denosumab treatment, a statistically significant decrease was detected in the phosphorus (p=0.022) and alkaline phosphatase (p<0.001) levels of the patients. Improvement was observed in BMD (gr/cm^2) values of L1-L4 (from 0.887 to 0.933), femoral neck (from 0.693 to 0.727), and total hip (from 0.762 to 0.782) regions with denosumab treatment. Similarly, the patients' BMD Z scores and T scores were improved. Also, the denosumab-related adverse event was not observed.

Conclusions: In this study, treatment characteristics of osteoporosis patients were retrospectively examined. Denosumab was well tolerated in patients, and no serious treatment-related side effects were detected. After bisphosphonate use, denosumab was shown to be an effective and safe treatment option in the treatment of osteoporosis.

Keywords: Osteoporosis, bisphosphonate, denosumab

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INTRODUCTION

Osteoporosis is a bone disease with decreased bone mineral density, microarchitectural disruption, and an increased risk of bone fracture. Many risk factors have been identified for the development of osteoporosis, including drug use, endocrine diseases, nutritional disorders, gastrointestinal absorption disorders, and genetic diseases. In order to find the cause of osteoporosis, a differential diagnosis should be made with past medical history and biochemical values such as calcium, phosphorus, alkaline phosphatase, and vitamin D levels. Osteoporosis is asymptomatic, and there is no pain in the patients until developing to the deformity associated with a bone fracture. The diagnosis of osteoporosis is made by increasing the fragility of the bones or by determining the T score below -2.5 by bone mineral density (BMD) measurement by dual-energy x-ray absorptiometry (DEXA) (1). Many lifestyle-related factors, such as calcium/vitamin D replacement, diet, exercise, and smoking cessation are effective in improving bone mineral density in the treatment of osteoporosis (2-5).

Osteoporosis treatment with pharmacological agents is recommended in postmenopausal women with a T-score of ≤-2.5 in BMD measurement or a history of fragility fracture (6). In addition to calcium/vitamin D replacement, the most commonly used treatment agents in the treatment of osteoporosis are bisphosphonate group drugs that inhibit bone resorption, such as zoledronic acid, risedronate, and alendronate (7). Denosumab can be used in the treatment of osteoporosis, especially in older people with a high risk of fracture, in patients with a contraindication to the use of bisphosphonates or who do not benefit sufficiently from bisphosphonate therapy. Denosumab is a monoclonal antibody that inhibits nuclear factor kappa-B ligand (RANKL) and thus inhibits bone resorption by inhibiting osteoclast formation and activation (8). Denosumab is not generally recommended for first-line therapy in patients with osteoporosis and in premenopausal patients. This study aimed to evaluate the efficacy and safety of denosumab treatment in patients with osteoporosis who had previously used bisphosphonates and did not benefit enough in the Turkish population.

MATERIAL AND METHODS

Patients and data collection

A retrospective observational design was used to create this study. Prior to conducting the study, approval from the ethics committee was obtained, and good clinical practice principles were followed. Patients diagnosed and treated in the single tertiary endocrinology outpatient clinic between 2018 and 2022 were involved in the study. The patients included in the study were identified by scanning the patients who received denosumab with the diagnosis of osteoporosis via the hospital data processing system. Inclusion criteria were determined as 1- being female, 2- having a diagnosis of osteoporosis, and 3- using bisphosphonates before denosumab. All patients had used bisphosphonates regularly and had not responded to treatment. Patients with insufficient follow-up data for analysis and male patients were excluded from the study. The diagnosis of osteoporosis was accepted as a BMD T score of ≤-2.5, which is also accepted by the World Health Organization. Demographic characteristics, medical histories, menopause status, and treatment characteristics of the patients were recorded. Biochemical parameters such as parathormone (PTH), creatine, calcium, phosphorus, albumin, vitamin D, alanine transaminase (ALT), and alkaline phosphatase (ALP) levels were noted.

The patients used denosumab (PROLIA®, Amgen, USA) 60 mg every six months. Each patient was given vitamin D 800 IU and calcium 1200-1500 mg (except for patients with hyperparathyroidism) daily. In all patients, lumbar vertebrae 1 (L1), lumbar vertebrae 2 (L2), lumbar vertebrae 3 (L3), lumbar vertebrae 4 (L4), lumbar vertebrae 1-4 (L1-L4), lumbar vertebrae 2-4 (L2-L4), femoral neck, and total hip BMD measurements were made with DEXA at baseline and after denosumab treatment. Baseline BMD (pre-denosumab) and 1st year BMD (post-denosumab) T scores, Z scores, and bone densities (gr/cm2) were compared, and improvement under denosumab was evaluated. In addition, treatment-related side effects were recorded.

Statistical analysis

The statistics of the study were performed via SPSS 29 (IBM, Armonk, NY, USA). Continuous variables in the study were represented by median (as well as minimum and maximum values) value numbers and percentages, while categorical variables were described by numbers and percentages. Paired sample t-test was done to assess pre-and post-BMD outcomes and biochemical values. When the p-value was less than 0.05, results were deemed statistically significant, and the probability ratio was calculated.

RESULTS

Patient characteristic

Sixty-three patients using denosumab with the diagnosis of osteoporosis were identified, and statistical analyses were performed with the data of 55 patients who met the study criteria. All patients included in the study were women. The median age of the patients was 69 (46-90), and the median follow-up period was 14 (12-36) months. All patients included in the study were postmenopausal. The most common comorbidities in the patients were hypertension (56.4%), diabetes mellitus (27.3%), and hypothyroidism (30.9%). Fourteen (25.5%) patients had a history of fracture. The most common cause of osteoporosis was postmenopausal (56.4%), and the most common cause among secondary causes was primary hyperparathyroidism (14.5%). The general features of the patients are shown in Table 1.

Treatment modality and results

All patients had used bisphosphonates (median 24 months) before denosumab treatment. All patients received concurrent vitamin D and calcium replacement with denosumab therapy. No hypocalcemia or any adverse events associated with the use of denosumab were observed. When the basal BMD characteristics of the patients were examined, the median L1-L4 T score was -2.34 before the treatment, and the median value

Table 1. Patients Characteristics

	Number of Patients (Total:55)	(%)
Age at diagnosis		
65<	14	25.5
65 ≥	41	74.5
Medical history of endocrine disease		
Hypertension	31	56.3
Diabetes Mellitus	15	27.3
Chronic Kidney Disease	8	14.5
Hypothyroidism	17	30.9
Hyperthyroidism	4	7.3
Fracture history		
Yes	14	25.5
No	41	74.5
Osteoporosis type		
Senile	4	7.3
Postmenopausal	31	56.4
Secondary	20	36.4
Secondary causes of osteoporosis		
No	35	63.6
Hyperparathyroidism	8	14.5
Hypogonadism	4	7.3
Steroid use	4	7.3
Other	4	7.3

of the total hip T score was -2.53. Improvement was observed in BMD (gr/cm2) values of L1-L4 (from 0.887 to 0.933), femoral neck (from 0.693 to 0.727), and total hip (from 0.762 to 0.782) regions with denosumab treatment. The basal BMD values of the patients by region are shown in Table 2. When the changes in biochemical values were examined, it was determined that the mean vitamin D level of the patients increased by 10.8 ng/mL compared to before denosumab in the post-denosumab period. In addition, it was observed that the serum phosphorus level (p=0.022) and ALP level (p<0.001) decreased statistically significantly (Table 3). After denosumab treatment, in BMD measurement, L1-L4 (p=0.003), L2-L4 (p=0.001), femur neck (p=0.017), and femur total (p<0.001) T scores were improved (Table 4). In the evaluation made in terms of the BMD Z score, there was an additional improvement in the L2 (p=0.006) Z score, and the improvement in the femoral neck (p=0.068) Z score not remained within the statistical limit (Table 5). In addition, bone densities showed a general statistically

Table 2. BMD characteristics of patients pre- and post-denosumab treatment

	T Scores				Z scores				BMD (gr/cm²) levels			
	Mean	N	SD	SEM	Mean	N	SD	SEM	Mean	N	SD	SEM
L1 Post-denosumab	-2.407	40	1.682	0.266	-0.877	39	1.905	0.305	0.840	40	0.201	0.031
Pre-denosumab	-2.418	40	1.517	0.239	-1.049	39	1.661	0.266	0.845	40	0.179	0.028
L2 Post-denosumab	-2.600	36	2.432	0.405	-0.979	39	1.584	0.253	0.907	40	0.180	0.028
Pre-denosumab	-2.625	36	1.497	0.249	-1.495	39	1.626	0.260	0.868	40	0.185	0.029
L3 Post-denosumab	-1.711	38	1.599	0.259	-0.586	36	1.468	0.244	0.999	40	0.219	0.034
Pre-denosumab	-2.213	38	1.346	0.218	-0.981	36	1.525	0.254	0.955	40	0.211	0.033
L4 Post-denosumab	-1.672	39	1.489	0.238	-0.314	37	1.505	0.247	1.011	40	0.219	0.034
Pre-denosumab	-2.082	39	1.397	0.223	-0.689	37	1.642	0.270	0.970	40	0.197	0.031
L1-L4												
Post-denosumab	-2.010	52	1.540	0.213	-0.518	39	1.625	0.260	0.933	52	0.185	0.025
Pre-denosumab	-2.344	52	1.422	0.197	-0.941	39	1.546	0.247	0.887	52	0.179	0.024
L2-L4												
Post-denosumab	-1.934	47	1.393	0.203	-0.464	36	1.512	0.252	0.975	49	0.191	0.027
Pre-denosumab	-2.353	47	1.351	0.197	-0.856	36	1.522	0.253	0.915	49	0.190	0.027
Femure Neck												
Post-denosumab	-2.352	54	0.684	0.093	-0.585	41	0.768	0.120	0.727	54	0.086	0.011
Pre-denosumab	-2.539	54	0.687	0.093	-0.815	41	0.825	0.128	0.693	54	0.076	0.010
Total Hip												
Post-denosumab	-1.806	54	0.874	0.119	-0.407	41	0.864	0.135	0.782	53	0.091	0.012
Pre-denosumab	-2.539	54	0.687	0.093	-0.707	41	0.815	0.127	0.762	53	0.084	0.011

N: Number, SD: Standart deviation, SEM: Standart Error Mean, CI: Confidence Interval

Table 3. Comparison of patients' pre- and post-denosumab biochemical values

Paired differences							
				95% CI of the difference		T-test value	Sig (two -tailed)
	Mean	SD	SEM	Lower	Upper		
Parathormone (pg/mL) Post- Parathormone (pg/mL) Pre	-9.217	65.321	13.620	-37.464	19.029	-0.677	0.506
Creatine (mg/dL) Post- Creatine (mg/dL) Pre	-0.238	2.005	0.280	-0.802	0.325	-0.850	0.399
Calcium (mg/dL) Post- Calcium (mg/dL) Pre	0.005	0.540	0.075	-0.146	0.1580	0.078	0.938
Phosphorus (mg/dL) Post- Phosphorus (mg/dL) Pre	-0.214	0.582	0.089	-0.395	-0.032	-2.386	0.022
Albumin (g/dL) Post- Albumin (g/dL) Pre	0.596	3.622	0.528	-0.468	1.659	1.128	0.265
Vitamin D level (ng/mL) Post- Vitamin D level (ng/mL) Pre	10.820	49.561	7.080	-3.415	25.056	1.528	0.133
ALT (U/L) Post – ALT (U/L) Pre	-1.092	7.867	1.112	-3.328	1.143	-0.982	0.331
ALP (U/L) Post – ALP (U/L) Pre	-17.905	18.743	4.090	-26.436	-9.373	-4.378	<0.001

SD: Standart deviation, SEM: Standart Error Mean, CI: Confidence Interval

Table 4. Comparison of patients' pre- and post-denosumab BMD T scores

	Paired differences						
				95% CI of the difference		T-test value	Sig (two-tailed)
	Mean	SD	SEM	Lower	Upper		
L1 Post- L1 Pre	0.010	1.126	0.178	-0.350	0.370	0.056	0.956
L2 Post- L2 Pre	0.025	2.356	0.392	-0.772	0.822	0.064	0.950
L3 Post- L3 Pre	0.502	1.043	0.169	0.159	0.845	2.969	0.005
L4 Post- L4 Pre	0.410	1.097	0.175	0.054	0.765	2.335	0.025
L1-4 Post- L1-4 Pre	0.334	0.767	0.106	0.121	0.548	3.144	0.003
L2-4 Post- L2-4 Pre	0.419	0.819	0.119	0.178	0.659	3.508	0.001
Femoral Neck Post-Femoral Neck Pre	0.187	0.557	0.075	0.034	0.339	2.466	0.017
Total Hip Post- Total Hip Pre	0.733	0.792	0.107	0.517	0.949	6.803	<0.001

SD: Standart deviation, SEM: Standart Error Mean, CI: Confidence Interval

Table 5. Comparison of patients' pre- and post-denosumab BMD Z scores

	Paired differences						
				95% CI of the difference		T-test value	Sig (two-tailed)
	Mean	SD	SEM	Lower	Upper		
L1 Post- L1 Pre	0.171	1.058	0.169	-0.171	0.514	1.014	0.317
L2 Post- L2 Pre	0.515	1.115	0.178	0.153	0.877	2.885	0.006
L3 Post- L3 Pre	0.394	0.763	0.127	0.136	0.652	3.099	0.004
L4 Post- L4 Pre	0.375	1.032	0.169	0.031	0.720	2.213	0.033
L1-4 Post- L1-4 Pre	0.423	0.881	0.141	0.137	0.708	2.997	0.005
L2-4 Post- L2-4 Pre	0.391	0.707	0.117	0.152	0.631	3.321	0.002
Femoral Neck Post-Femoral Neck Pre	0.229	0.781	0.122	-0.017	0.475	1.879	0.068
Total Hip Post- Total Hip Pre	0.300	0.413	0.064	0.169	0.430	4.645	0<0.001

SD: Standart deviation, SEM: Standart Error Mean, CI: Confidence Interval

Table 6. Comparison of patients' pre- and post-denosumab BMD levels

	Paired differences					T-test value	Sig (two-tailed)
				95% CI of the difference			
	Mean	SD	SEM	Lower	Upper		
L1 Post- L1 Pre	-0.004	0.133	0.021	-0.047	0.038	-0.211	0.834
L2 Post- L2 Pre	0.038	0.126	0.019	-0.001	0.078	1.932	0.061
L3 Post- L3 Pre	0.044	0.176	0.027	-0.012	0.100	1.581	0.122
L4 Post- L4 Pre	0.041	0.135	0.021	-0.001	0.084	1.933	0.060
L1-4 Post- L1-4 Pre	0.046	0.096	0.013	0.019	0.072	3.428	0.001
L2-4 Post- L2-4 Pre	0.060	0.099	0.014	0.031	0.088	4.233	<0.001
Femoral Neck Post-Femoral Neck Pre	0.033	0.073	0.009	0.013	0.053	3.401	0.001
Total Hip Post-Total Hip Pre	0.020	0.054	0.007	0.005	0.035	2.784	0.007

SD: Standart deviation, SEM: Standart Error Mean, CI: Confidence Interval

significant improvement except for L1 (Table 6). During the follow-up period, no patients had any symptomatic fractures detected.

DISCUSSION

Osteoporosis is a common public health problem in postmenopausal women, especially in the elderly. Morbidity due to osteoporosis-related bone fractures can cause severe social and psychogenic difficulties for patients. Although it is tried to prevent the development of osteoporosis with lifestyle changes and calcium and vitamin D supplementation, in some cases, pharmacological treatments are needed. This study showed real-life outcomes of denosumab after bisphosphonate use in patients with osteoporosis at a single endocrinology center. Denosumab was found effective and safe in the treatment of osteoporosis in this study. In the FREEDOM study, patients with postmenopausal osteoporosis were evaluated, and after three years of follow-up, it was shown that denosumab treatment reduced the risk of new vertebral (2.3 vs. 7.2 percent), total hip (0.7 vs. 1.2 percent) and nonvertebral (6.5 vs. 8.5 percent) fractures compared to placebo (9). In addition, in the FREEDOM study, the BMD density of the patients increased, and bone turnover markers levels decreased. In a phase 3 study comparing the efficacy of denosumab and alendronate in postmenopausal women with osteoporosis, it was found that denosumab increased BMD in all bone regions measured and significantly decreased bone turnover markers compared to alendronate (10). In another study, patients who used alendronate for at least six months and continued alendronate were compared with patients who were switched to denosumab; a 1.90% increase in total hip BMD was found in patients in the denosumab arm, and also a statistically significant improvement in the lumbar spine, femoral neck, and 1/3 radius regions was achieved (11). After the use of bisphosphonate, denosumab provides an improvement in at least one of the DEXA T or Z scores, and BMD measurements in other regions except for the L1 region in this study. The lack of statistically significant improvement in the L1 vertebra in this study may be explained by the limited number of patients and the duration of treatment. The number of studies comparing denosumab with bisphosphonates in clinical practice is limited, and a comparative study with an endpoint of fracture risk reduction is not available in the literature. Therefore, there are some controversial issues with the optimal use of denosumab therapy. Due to the ease of oral use of bisphosphonates and their low cost, bisphosphonates are primarily used in the first series in the treatment of osteoporosis in clinical practice, and denosumab is used after the use of bisphosphonates. Terminating denosumab treatment in a short time may increase the risk of multiple fractures in the vertebral bones (12-14). Therefore, patients who will be started on denosumab should be evaluated in terms of treatment compliance.

Denosumab is generally well tolerated, and side effects are rare. The risk of denosumab-associated hypocalcemia is less than 1% and is especially seen in patients with hyperparathyroidism, malabsorption syndrome, and chronic kidney disease (15). Since denosumab impairs bone remodeling, long-term side effects such as jaw necrosis and atypical fractures can be seen rarely (16). It has also been shown that denosumab-related bone healing may be delayed, and this may affect other wound-related complications (17). In this study, no adverse events were observed in the patient group under denosumab treatment. This may be explained by the limited number of patients involved in the study and the rare occurrence of denosumab-related side effects. As a result of being retrospective, this study had some limitations. The patients number was relatively limited, and some patients' data were missing. The patient group involved in the study was heterogeneous.

CONCLUSIONS

In this study, it showed that using denosumab after bisphosphonate use in patients with osteoporosis in the Turkish population is effective and safe. Also, it was detected the osteoporotic patients profile used denosumab after bisphosphonate in the Turkish population. This study contributes to the literature in terms of demonstrating the effectiveness of denosumab in the Turkish population with osteoporosis. Osteoporosis is a bone disease that is affected by many environmental factors. In the future, a better

understanding of the development processes of osteoporosis will shed light on the development of new advances in terms of both prevention and treatment of osteoporosis.

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