

Denosumab Discontinuation Rate in Patients Who Presented with Osteoporotic Vertebral Fracture During Pandemic

Pandemi Sırasında Osteoporotik Vertebral Kırıkla Başvuran Hastalarda Denosumab Bırakma Oranı

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Abstract

Objective: Social distancing mitigates transmission of Coronavirus disease-2019 but also can delay access to parenteral osteoporosis therapy. After discontinuation of denosumab therapy without concomitant biphosphanate use results with increased rate of multiple vertebral fractures within 2 to 10 months.

Methods: In this study, we wanted to evaluate whether restrictions during the pandemic resulted in an increased fracture rate due to denosumab discontinuation. For this, we compared the data between 2020-2021, when the restrictions were the most intense, and 2022-2023, when the restrictions were relaxed. Prospectively collected data of patients who applied to the neurosurgery clinic with osteoporotic vertebral fractures between 2020-2021 and 2022-2023 were retrospectively analyzed.

Results: A total of 49 patients were met the inclusion criteria, denosumab discontinuation was detected in five patients who presented with osteoporotic fractures during the period of intense restrictions, there was no patients with denosumab discontinuation during the period when the restrictions were relaxed. Discontinuation reasons was due to fear of access to hospital and mobility restriction in all patients. Mean time interval between treatment discontinuation and fracture occurrence was 12.6 months (10-15 months).

Conclusion: Patients should be warned about the durability of denosumab treatment, and if there is doubt about the durability, oral bisphosphonate therapy should be temporarily switched in pandemic.

Keywords: Pandemic, denosumab, vertebral fracture

Öz

Amaç: Sosyal mesafe, Koronavirüs hastalığı-2019'un bulaşmasını azaltır ancak aynı zamanda parenteral osteoporoz tedavisine erişimi geciktirebilir. Eş zamanlı bifosfanat kullanımı olmaksızın denosumab tedavisinin kesilmesi, iki ila on ay içinde çoklu vertebral kırık oranlarında artış ile sonuçlanır.

Yöntem: Bu çalışmada pandemi sırasındaki kısıtlamaların denosumab tedavisini kesilmesine bağlı olarak kırık oranında artışa yol açıp açmadığının değerlendirilmesi amaçlandı. Bunun için kısıtlamaların en yoğun olduğu 2020-2021 ile kısıtlamaların gevşetildiği 2022-2023 arasındaki veriler karşılaştırıldı. 2020-2021 ve 2022-2023 yılları arasında nöroşirürji kliniğine osteoporotik vertebral kırığı ile başvuran hastaların prospektif olarak toplanan verileri retrospektif olarak incelendi.



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Öz

Bulgular: Toplam 49 hasta dahil edilme kriterlerini karşıladı, kısıtlamaların yoğun olduğu dönemde osteoporotik kırıkla başvuran beş hastada gecikmiş denosumab enjeksiyonu saptandı, kısıtlamaların gevşetildiği dönemde denosumab tedavisinin kesildiği hasta yoktu. Tedaviyi bırakma nedenleri tüm hastalarda hastaneye erişim korkusu ve sokağa çıkma kısıtlılığıydı. Tedavinin kesilmesi ile kırık oluşumu arasındaki ortalama süre 12,6 ay (10-15 ay) idi.

Sonuç: Hastalar denosumab tedavisinin devamlılığı konusunda uyarılmalı ve devamlılık konusunda şüphe varsa pandemide oral bifosfonat tedavisine geçici olarak dönülmelidir.

Anahtar Kelimeler: Pandemi, denosumab, omurga kırığı

Introduction

Osteoporotic fracture is a public health issue affecting thirty percent of women and is associated with high morbidity and mortality rates⁽¹⁾. Vertebral fracture-associated pain and limitation of function can cause decreased health-related quality of life in the elderly population⁽¹⁾.

Healthcare systems are overstretched during the pandemic, resulting in reduced hospital and doctor visits. In addition, social distancing mitigates transmission of Coronavirus disease-2019 (COVID-19) and can delay access to parenteral therapies. The management of osteoporosis is largely performed in outpatient settings. The prescribing and administration of anti-osteoporosis drugs may have been disrupted by the COVID-19 pandemic. A retrospective analysis using Google Analytics data found that access to the online FRAX® fracture risk assessment tool was almost 60% lower in April than in February 2020, which may indicate the neglect of osteoporosis assessment during the pandemic⁽²⁾. In another study, as concrete proof of this, it was shown that only 29% of the patients could perform follow-up bone mineral density assessment with dual energy X-ray absorptiometry (DXA) during the pandemic period, and only 60% of the patients could continue their parenteral anti-osteoporosis treatment⁽³⁾.

Agents used for treating osteoporosis can simply be divided into two groups: Anabolic and antiresorptive. Bisphosphonates and denosumab are currently used as antiresorptive agents. After discontinuation of bisphosphonates, the antiresorptive effect lasts for 1-5 years; however, discontinuation of denosumab therapy without concomitant bisphosphonate use results in accelerated bone loss and an increased rate of multiple vertebral fractures within 2 to 10 months⁽⁴⁻⁶⁾. Therefore, patients must be informed that denosumab therapy should not be discontinued without concomitant bisphosphonate use. Restricting access to parenterally administered denosumab during the pandemic period may increase the risk of fracture due to drug discontinuation⁽⁷⁾.

In this study, we aimed to evaluate whether restrictions during the pandemic resulted in an increased fracture rate due to denosumab discontinuation. For this, we compared the data between 2020 and 2021, when the restrictions were the most intense, and 2022 and 2023, when the restrictions were relaxed.

Materials and Methods

Patients with an osteoporotic vertebral fracture who were admitted to the Neurosurgery Clinic between 2020 and 2021 and 2022-2023 in am and University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital were retrospectively analyzed. Patients were grouped as admitting to hospital between 2020 and 2021, when the restrictions were the most intense, and 2022 and 2023, when the restrictions were relaxed. The two groups compared their demographic data, clinical and laboratory findings, and osteoporotic treatment discontinuation.

Study Group

Postmenopausal women aged 50 years or older were included in the study. The other inclusion criteria were a conclusive clinical and radiological diagnosis of osteoporotic fracture with recent onset of back pain (less than one month).

Patients who were immobile and diagnosed with chronic inflammatory or oncologic diseases or with a history of neuroendocrine disorders (thyroid, parathyroid disorders, anticonvulsant- thiazolidinedione usage, etc.), chronic renal or liver diseases, and excessive use of systemic corticosteroids and alcohol were excluded. Male patients were also excluded to avoid bias because secondary predisposing factors for osteoporosis can be identified in 40-60% of men with osteoporotic fractures⁽⁸⁾.

Definition of Osteoporotic Vertebral Fracture

Clinic definition: Occurring a fall from a standing height or less without significant trauma⁽⁹⁾.

Radiological definition: Alteration appears in the shape and size of the vertebral body, associated or not with vertebral height loss, resulting as a wedge, end-plate (mono-or biconcave), or collapse vertebral deformity⁽⁹⁾.

Identification Methods for Vertebral Fractures

All patients in the study group had DXA images. In addition, all patients underwent thoracic or lumbar magnetic resonance or computed tomography imaging at hospitalization.

Statistical Analysis

The patients' files were reviewed retrospectively, and the demographic data, imaging and laboratory results, concomitant disease, and drug use were recorded. Analyses were performed using SPSS 22.0 (SPSS Inc, Chicago, IL). Normally distributed continuous variables are presented as mean \pm standard deviation and compared using Student's t-test. A p-value <0.05 was considered statistically significant for all statistical evaluations.

Results

Between 2020 and 2021, a total of 41 patients presented with osteoporotic vertebral fractures, and 24 patients met the inclusion criteria. The mean age was 73.3 ± 6.7 years, mean 25-hydroxy vitamin D level was 18.3 ± 8.1 ng/mL, and mean femoral neck BMD was 0.663 ± 22.42 g/cm². Regarding concomitant diseases, 16 (66.6%) patients had hypertension, two had type 2 (8.3%) diabetes, and four (16.6%) had anxiety disorder. Four patients (16.6%) had fractures in more than one vertebra. The T12 vertebra was the most common fracture site [six (25%) patients]. Vertebroplasty was performed in 10 patients and kyphoplasty in five patients. Other patients were followed up conservatively.

Between 2022 and 2023, a total of 43 patients presented with osteoporotic vertebral fractures, and 25 patients met the

inclusion criteria. The mean age was 72.1 ± 6.2 years, mean 25-hydroxy vitamin D level was 19.1 ± 7.1 ng/mL, and mean femoral neck BMD was 0.658 ± 18.33 g/cm². There were 14 (56%) patients with hypertension, four (16%) with type 2 diabetes, six (24%) with anxiety disorder, and two (8%) with coronary arterial disease. Six patients (24%) had fractures in more than one vertebra. The L1 vertebra was the most common fracture site [eight (32%) patients]. Vertebroplasty was performed in 12 patients and kyphoplasty in six patients. Other patients were followed up conservatively. There was no previous vertebral fracture history in either group. Comparison of the continuous variables summarized in Table 1.

When evaluated regarding medication use for osteoporosis, none of the patients in the 2022-2023 group had antiresorptive or anabolic agent use before admission. In the 2020-2021 group, two patients were using intravenous ibandronate, and five were using denosumab before presentation, and all patients had stopped using denosumab and ibandronate after the pandemic because of fear of access to hospital and mobility restriction. None of the patients in the denosumab discontinuation group were informed before treatment that denosumab therapy should not be discontinued without concomitant bisphosphonate use. The duration of antiresorptive therapy and time elapsed between the occurrence of vertebral fracture and antiresorptive therapy discontinuation are reported in Table 2.

Clinical and laboratory findings of the treatment discontinuation group are summarized in Table 3.

None of the patients in the study groups had a previous history of vertebral fracture or oral bisphosphonate and teriparatide usage. In addition, no other antiresorptive therapy or teriparatide was used before the current therapy in the discontinuation group.

Table 1. Comparison of age, 25-hydroxy vitamin D level, and femur BMD score between the groups

Variables	2020-2021	2022-2023	p-value
Age (years)	73.3 \pm 6.7	72.1 \pm 6.2	0.545
25-hydroxy vitamin D level (ng/mL)	18.3 \pm 8.1	19.1 \pm 7.1	0.599
Mean femoral neck BMD (g/cm ²)	0.663 \pm 22.42	0.658 \pm 18.33	0.433
Number of multiple fractures (n)	4	6	0.634
The most common fractured vertebra	T12	L1	-
Number of vertebroplast	10	12	0.678
Number of kyphoplasty procedures	5	6	0.712

Patient	Age	Drug	Length of therapy (months)	Time interval between treatment discontinuation and fracture occurrence (months)
1	65	Ibandronate	12	14
2	74	Ibandronate	15	15
3	83	Denosumab	18	11
4	72	Denosumab	24	13
5	77	Denosumab	12	10
6	74	Denosumab	12	15
7	76	Denosumab	30	14

Age (years)	74.4±5.4
Mean femoral neck BMD (g/cm ²)	0.621±113
25-hydroxy vitamin D level (ng/mL)	19.14±5.42
Concomitant diseases (n)	
Hypertension	1
Type 2 diabetes mellitus	2
Having a fracture in more than one vertebra (n)	0
Fracture management (n)	
Vertebroplasty	2
Conservatively	3
Average duration of denosumab use (months)	20±8
Average duration of ibandronate use (months)	24±11

Discussion

In our study, we detected denosumab discontinuation in five patients who presented with osteoporotic fractures during intense restrictions; there were no patients with denosumab discontinuation during the period when the restrictions were relaxed. Delayed denosumab dosing due to patient non-compliance is common in clinical practice, especially as the treatment extends beyond the first 1 to 2 years^(10,11). The average duration of denosumab use was 20±8 months in our study, but discontinuation was due to fear of access to hospital and mobility restriction in all patients, which are the main problems arising with the pandemic. It has been reported that there may be problems in accessing injectable osteoporosis treatments during the pandemic; therefore, the American Society for Bone and Mineral Research recommends the temporary transition to an oral bisphosphonate for patients at risk for delayed denosumab injection^(7,12).

The increased risk of bone loss and fracture after denosumab discontinuation without concomitant bisphosphonate use is a well-known complication. Lyu et al.⁽¹¹⁾ found that delayed denosumab administration by more than 16 weeks is associated with an increased risk of vertebral fracture. In another study examining the effect of delayed denosumab injection on BMD during the pandemic, BMD loss was evident nine months after the last injection⁽¹³⁾. Minisola et al.⁽¹⁴⁾ reported 12 patients admitted with osteoporotic vertebral fracture due to delayed denosumab injection during the pandemic. There were only eight cases the seven years before the pandemic⁽¹⁴⁾. In our study, the mean time interval between treatment discontinuation and fracture occurrence was 12.6 months (10-15 months).

Beneficial effects on bone mass persist 1-2 years after ibandronate discontinuation⁽¹⁵⁾. In our study, there were two patients with ibandronate discontinuation, and the time interval between treatment discontinuation and fracture occurrence was 14.5 months. Therefore, it may be unrealistic to attribute vertebral fracture development to ibandronate discontinuation in these patients.

We restricted inclusion criteria in order not to create bias, exclude secondary osteoporosis and etiologies other than discontinuation of denosumab, and balance continuous variables between groups. Although it was clearly seen in our study that the fracture rate due to denosumab discontinuation increased during intense restrictions, it is necessary to conduct a cohort study with a wider time interval to reach a definite conclusion.

Study Limitations

The major limitations of this study are its limited time period, its conduct only in osteoporotic patients presenting with fractures, and its retrospective design.

Conclusion

Patient compliance and treatment durability should be considered when choosing drugs during the pandemic. Patients should be warned about the durability of denosumab treatment, and if there is doubt, they should be temporarily switched to oral bisphosphonate therapy.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (no: 2022.04.120, KAEK/2022.04.120).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: B.E., Y.K., Concept: U.S., Design: U.S., Data Collection or Processing: Ş.B., Y.K., Analysis or Interpretation: U.S., B.E., Literature Search: U.S., Writing: U.S.

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