

# Retrospective Analysis of the Effects of Non-Compliance with Denosumab on Changes in Bone Mineral Density During the COVID-19 Pandemic

Chun-Feng Huang <sup>1,2</sup>  
Ming-Shi Shiao<sup>2</sup>  
Tso-Yen Mao<sup>3</sup>

<sup>1</sup>Department of Family Medicine, National Yang Ming Chiao Tung University Hospital, Yilan, Taiwan (Republic of China); <sup>2</sup>Department of Biomedical Sciences, Chang Gung University, Taoyuan, Taiwan (Republic of China); <sup>3</sup>Department of Leisure Services Management, Chaoyang University of Technology, Taichung, Taiwan (Republic of China)

**Purpose:** Although denosumab is a safe and effective treatment for osteoporosis in various clinical trials, few studies have investigated its efficacy in specific clinical situations. The effect of non-compliance with the standard six-month dosing regimen for denosumab on bone mineral density (BMD) was assessed in a retrospective study of patients prescribed denosumab during the COVID-19 pandemic.

**Patients and Methods:** Between February 2019 and September 2020, 638 patient records were reviewed, with 236 patients meeting the eligibility criteria. Patients were divided into three groups: those who received denosumab injections between five and seven months after their initial subcutaneous injection, those who received denosumab injections between seven and nine months after their initial subcutaneous injection, and those who received denosumab injections more than nine months after their initial subcutaneous injection. A multivariate regression study was conducted to compare the BMD shift (at least one year apart) before and after two denosumab injections between the three pre-specified groups in both the lumbar spine (LS) and the femoral neck (FN).

**Results:** The difference between LS BMD indicates that there is a statistical difference between subjects who received denosumab injections between 5 and 7 months (near-standard dosing interval) and more than 9 months ( $P=0.03$ ), but not in FN BMD, and no clinically significant association was identified.

**Conclusion:** The results of this study show that in special clinical situations, such as the COVID-19 pandemic, clinicians may have some flexibility to prescribe denosumab, but the interval between injections should not exceed 9 months.

**Keywords:** bone mineral density, compliance, COVID-19, denosumab, osteoporosis

## Introduction

As the global population ages, osteoporosis, a major public health problem, is becoming more prevalent.<sup>1-3</sup> Osteoporosis is characterized by low bone density, loss of bone tissue, and destruction of bone microarchitecture, all of which can contribute to reduced bone strength and an increased risk of fractures.<sup>4-6</sup>

Osteoporotic fractures, especially hip and vertebral fractures, are linked to high rates of morbidity and mortality in the elderly, as well as a major financial burden on the health-care system. Women are four times more likely than men to have osteoporosis, but some evidence suggests that men have more osteoporosis-related

Correspondence: Tso-Yen Mao  
Department of Leisure Services  
Management, Chaoyang University of  
Technology, 168, Jifeng E. Road, Wufeng  
District, Taichung, 413, Taiwan (Republic  
of China)  
Tel +886 4 23323000 #7453  
Fax +886 4 23742363  
Email tymao.research@gmail.com

complications.<sup>5,6</sup> In all countries, the incidence rate of hip and vertebral osteoporotic fractures increases exponentially with age.<sup>1,2</sup> Bisphosphonates are the most used drugs for treatment with osteoporosis.<sup>7</sup> Bisphosphonates have been shown to significantly minimize the risk of vertebral and hip fracture in osteoporotic patients. Unfortunately, some significant studies have found that most postmenopausal women discontinue the use of bisphosphonates during the first year of care.<sup>8,9</sup> A few patients may have interrupted their regular medications, including related osteoporosis treatments, because they were concerned about the possibility of side effects, such as osteonecrosis of the jaw, or the risk of infection when they returned to the clinic during the COVID-19 pandemic.<sup>8–11</sup> Impaired long-term compliance and durability of pharmacological therapy of osteoporosis may result in an increased risk of fractures.<sup>8</sup>

Denosumab is a human monoclonal antibody against the protein RANKL (receptor activator of nuclear factor- $\kappa$ B ligand) that has been shown in placebo-controlled clinical trials to minimize severe osteoporotic fractures in postmenopausal women at high risk of fracture.<sup>12–14</sup> In postmenopausal women, increased RANKL production has been associated with increased osteoclast activity and overall net bone resorption.<sup>7</sup> Denosumab binds to RANKL with high affinity and specificity, preventing it from binding to RANK (a nuclear factor- $\kappa$ B receptor activator) receptors on osteoclasts and osteoclast precursors, inhibiting the synthesis, function, and lifetime of established osteoclasts.<sup>14</sup> Denosumab, in turn, prevents bone resorption and remodeling, as measured by increased bone mineral density (BMD) and decreased porosity at all measured skeletal sites, as well as lowering biochemical markers for bone turnover.<sup>12–14</sup> Treatment with Denosumab subcutaneously once every six months is well tolerated in clinical trials and significantly reduces the risk of hip, non-vertebral and vertebral fractures.<sup>13,14</sup> Unlike impaired bisphosphonate compliance, which is only associated with increased fracture risk, there is concern that rebound activation of bone turnover following denosumab discontinuation will result in fractures, particularly multiple vertebral fractures.<sup>15</sup> In a group of 70 women who had numerous spontaneous vertebral fractures after discontinuing denosumab, a median of five vertebral fractures occurred 7 to 20 months following the last denosumab injection.<sup>15</sup>

Low adherence to anti-osteoporosis drugs is unable to achieve optimal therapeutic results.<sup>16</sup> This study aimed to see how non-compliance with denosumab affected BMD

(measured on the lumbar spine [LS] and femoral neck [FN]) during the COVID-19 pandemic compared to patients who followed a near-standard dosing schedule.

## Patients and Methods

### Participants in the Study

Patients undergoing denosumab treatment and duration of treatment were studied in this retrospective chart analysis. All patients have been screened for eligibility. A total of 638 patient records were checked from February 2019 to September 2020, with 236 patients meeting the participation requirements. Patients were eligible for this study if they were over 50 years of age, had two subcutaneous denosumab injections, and had two sequential BMD measurements (at least one year apart) before and after two denosumab injections. Besides, subjects included in the study had never been treated with oral bisphosphonates (risedronate or alendronate), intravenous bisphosphonates (zoledronic acid), raloxifene, or teriparatide. If two BMD measurements were taken with different DXA (dual-energy x-ray absorptiometry) equipment (Prodigy; GE Medical Systems Lunar, Madison, WI, USA, or Discovery; Hologic scanner, Bedford, MA, USA) if a fracture in the femoral neck and/or lumbar spine occurred between two denosumab injections, the subject was excluded.

### Protocol on Intervention

Patients were categorized based on adherence to denosumab: receiving the following injection (1) between 5 and 7 months; (2) between 7 and 9 months; and (3) more than 9 months after the initial subcutaneous injection. The time-frame between the initial and subsequent injections of denosumab was used to determine compliance. Patients were considered to comply if the two denosumab injections were 5–7 months apart. Prevalent and incident fracture data were collected from the patient's medical records. Fractures were considered incidental if they occurred during the period of the retrospective review. All multivariate regression analyses were adjusted based on baseline BMD values, age, medical history, and the number of months between two BMD measurements.

### Ethics

This study was approved by the Institutional Review Board (IRB) of the National Yang-Ming University Hospital (YMUH2020A006) in accordance with the Declaration of Helsinki. The study involves no prospectively collected

data so there is no access to patients or opportunity to seek informed consent. A waiver of consent was approved by IRB as re-contacting this number of patients to obtain informed consent would be impracticable. The study is no greater than minimal risk and will have no direct impact on patient's rights and clinical care. Finally, we guarantee the confidentiality of all patient data.

## Statistical Analysis

Descriptive statistics were used to summarize the basic characteristics. IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA) was used to conduct formal statistical studies. Multivariable regression tests for both LS and FN were used to evaluate differences in BMD change ( $\text{g/cm}^2$ ) between the three pre-specified groups with two denosumab injections. The reference group was considered to have had a follow-up injection of between 5 and 7 months. The minimum total sample size in this study is 77, with at least 20 subjects for each independent variable, for an effect size of  $f^2=0.15$ , power=0.8, and  $\alpha=0.05$ .

## Results

Of the 638 charts studied, 215 females (91.1%) and 21 males (8.9%) were eligible for osteoporosis with denosumab therapy and DXA scan. The average age and standard deviation (SD) of patients were 68.5 (9.7) years. The baseline BMD of the lumbar spine and femoral neck was 0.803 (0.118) and 0.722 (0.109)  $\text{g/cm}^2$ , respectively. Before treatment with denosumab, 21.19% of patients had at least one non-vertebral fracture, while 30.08% had a history of vertebral fracture. At the end of the analysis, patients were categorized into three groups based on their compliance with denosumab therapy. Demographic data are shown in Table 1. 177 patients received a subsequent injection of denosumab for 5 to 7 months, 39 for 7 to 9 months, and 20 for more than 9 months. The baseline BMD results, as well as the history of non-vertebral and vertebral fractures, are provided for each of the categories identified. Furthermore, anticonvulsants, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and proton pump inhibitors have all been proposed as significant risk factors for osteoporosis, with their use studied in each category. Except for fracture history, there were no statistically significant differences in the three groups' basic characteristics.

Table 2 shows the comparative data after two denosumab injections. Descriptive statistics and BMD values were given after two denosumab treatments. The presence of incident fractures was also indicated. In patients who

received denosumab subsequently for 5 to 7 months, 7 to 9 months, and more than 9 months, the mean period and SD of treatment from the initial injection were 6.11 months (0.66), 7.95 months (0.58), and 11.15 months (1.26), respectively. Multivariate lumbar spine and femoral neck regressions were used to compare BMD improvement after two doses of denosumab therapy. The groups receiving a subsequent injection between 7 and 9 months and more than 9 months later were compared to the group receiving a subsequent injection between 5 and 7 months. Table 3 displays the results.

The variance of LS BMD alteration in patients differed between receiving subsequent injections after their initial injection for more than 9 months and between 5 and 7 months ( $-0.0191 \text{ g/cm}^2$ , 95% CI  $-0.0083$  to  $-0.0305$ ). However, the difference of LS BMD alteration between 7 and 9 months in patients receiving subsequent injections compared to the reference group receiving injections between 5 and 7 months was not statistically different ( $0.0007 \text{ g/cm}^2$ , 95% CI  $-0.0024$  to  $0.0031$ ). In contrast to the comparison group receiving an injection between 5 and 7 months after their initial injection, the difference in FN BMD variation was  $0.0068 \text{ g/cm}^2$  (95% CI  $-0.0155$  to  $0.0319$ ) for patients receiving a sequential injection between 7 and 9 months and  $-0.0044 \text{ g/cm}^2$  (95% CI  $-0.0151$  to  $0.0067$ ) for patients receiving a sequential injection more than 9 months. Despite the fact that no clinically significant association was found, the relationship between drug duration and change in LS BMD was significant ( $P=0.03$ ) if the subsequent injection of denosumab was less than or more than 9 months.

## Discussion

This study aims to see how far the failure to comply with denosumab affects the changes in BMD. In comparison to the hip bone, the vertebrae have more trabecular bones, which have a larger surface exposed to bone marrow and blood flow, and the turnover and response to denosumab are higher.<sup>14</sup> In this retrospective study, multivariate regressions revealed statistically significant differences only in LS BMD values, not FN BMD values, between patients who received subcutaneous denosumab injections between 5 and 7 months and more than 9 months. In other words, patients and clinicians should not wait longer than 9 months between injections of denosumab, because drug levels in circulation are steadily declining 6 months after administration, with the drug being completely removed at 9 months. Previous studies have shown that bone turnover

**Table 1** Baseline Characteristics of Participants Stratified by Denosumab Injection Time

Characteristic	Time of Subsequent Injection of Denosumab			P value
	5–7 Months	7–9 Months	>9 Months	
Sample size (n)	177	39	20	
Age, years, mean (SD)	68.50 (9.55)	66.88 (8.62)	65.14 (8.55)	0.23
Women, % (n)	91.53% (162)	92.31% (36)	85.0% (17)	0.19
Proton pump inhibitor (PPI) use, % (n)	25.99% (46)	25.64% (10)	30.00% (6)	0.21
Selective serotonin reuptake inhibitor (SSRI) use, % (n)	5.08% (9)	7.69% (3)	5.00% (1)	0.11
Serotonin-norepinephrine reuptake inhibitor (SNRI) use, % (n)	7.91% (14)	10.26% (4)	0.00% (0)	0.26
Tricyclic antidepressant (TCA) use, % (n)	1.69% (3)	5.13% (2)	10.00% (2)	0.19
Anticonvulsants use, % (n)	14.69% (26)	17.95% (7)	15.00% (3)	0.12
Glucocorticoids use, % (n)	0% (0)	0% (0)	0% (0)	
BMD, mean (SD)				
Lumbar spine	0.807 (0.109)	0.782 (0.095)	0.808 (0.101)	0.25
Femoral neck	0.729 (0.081)	0.692 (0.100)	0.719 (0.105)	0.23
History of non-vertebral fracture, % (n)	22.60% (40)	20.51% (8)	10.00% (2)	0.03
History of vertebral fracture, % (n)	29.38% (52)	30.77% (12)	35.00% (7)	0.03

**Table 2** Characteristics of Participants Stratified After Two Denosumab Injections

Characteristic	Time of Subsequent Injection of Denosumab			P value
	5–7 Months	7–9 Months	>9 Months	
BMD, mean (SD)				
Lumbar spine	0.847 (0.099)	0.823 (0.095)	0.829 (0.091)	0.31
Femoral neck	0.774 (0.089)	0.749 (0.092)	0.760 (0.102)	0.29
Incident non-vertebral fracture, % (n)	2.82% (5)	2.56% (1)	0.00% (0)	0.02
Incident vertebral fracture, % (n)	0.56% (1)	0.00% (0)	0.00% (0)	0.04
Mean duration of treatment from baseline injection in months (SD)	6.11 (0.66)	7.95 (0.58)	11.15 (1.26)	0.01

**Table 3** Regression Analysis Comparing Bone Mineral Density (BMD) Change Between Groups [Reference Group: 5–7 Months]\*

Groups: Time Between 1st and 2nd Injection Was		Estimate	95% Confidence Limits
Lumbar spine	Between 7–9 months	0.0007	–0.0024 to 0.0031
	More than 9 months	–0.0191	–0.0083 to –0.0305
Femoral neck	Between 7–9 months	0.0068	–0.0155 to 0.0319
	More than 9 months	–0.0044	–0.0151 to 0.0067

Notes: \*All multivariate regression analyses were adjusted for baseline BMD values, patient age, drugs with or without proton pump inhibitors, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, anticonvulsants, and the number of months between the initial and subsequent BMD after two denosumab injections.

markers generally reached pre-treatment levels within 9 months of the last dose of denosumab, but at re-initiation, reductions in CTX by denosumab were similar to those seen in patients receiving primary denosumab therapy.<sup>13,14.</sup>

The potency of treatment is based on the efficacy of therapy and adherence to the recommended dosing regimen.<sup>17,18</sup> Osteoporosis, like other chronic medical conditions, requires methods for keeping patients on

track of their treatment. Failure to comply with a regular bisphosphonate or denosumab therapy may result in lower BMD values and, as a result, a higher risk of fracture.<sup>19,20</sup> Denosumab is an approved treatment for osteoporosis, which slows the progression of the disease. It is a fully human monoclonal antibody that binds to the RANKL receptor activator, resulting in increased bone mineral density and reduced risk of fracture. Although the pharmacology of denosumab is promising, patients' compliance with existing clinical guidelines is critical to the efficacy of the drug as an osteoporosis treatment. This underlines the importance of determining the root causes of poor adherence and makes it possible to work towards improving clinical practice.

Many countries have had to make difficult decisions to protect their citizens in the face of the COVID-19 pandemic. These decisions include lockdowns and restrictions on people's movements, as well as the deployment of health personnel to the front lines of the COVID-19 outbreak. This could be a major issue for patients with chronic diseases, such as osteoporosis, who need to return for check-ups and prescription refills because access to health facilities and their attending physicians may be restricted. Furthermore, the increased risk of infection in hospitals has forced most patients to avoid physician consultations at their health facilities. This study suggests that delay is acceptable only during an unforeseen period (such as the COVID-19 pandemic) when denosumab injections cannot be given to the patient in a timely manner.<sup>10,11</sup> Otherwise, all patients should continue to receive the following doses every 6 months or at least no later than 9 months, based on the pharmacodynamics of denosumab.

Factors related to the properties and management of denosumab and group-specific factors for patients may explain what causes lower compliance rates. First, denosumab is only available by subcutaneous injection and can only be administered by medical professionals, and therefore whether the hospital environment is safe will affect the willingness of patients to receive injections during the COVID-19 pandemic. Second, physicians have a significant impact on the adherence of denosumab because they can set a dosing schedule, track regularity, and convey the importance of patient compliance when the injection is delayed. Moreover, a medical case manager may contact patients, for example, a week in advance of their next planned injection as a reminder. During the COVID-19 epidemic, however, these measures may be disrupted and cannot be carried out regularly.

After the COVID-19 pandemic, the study's most apparent weakness was the limited sample size. It is difficult to draw firm conclusions based on the small number of patients between 7–9 months and more than 9 months groups. Also, due to the limited number of incidents and the small scale of the collective, we are not able to comment on variations in fracture rates between groups. A larger cohort with a longer follow-up period in patients who are not adhering to therapy may show a difference in FN BMD or even fracture rates. Furthermore, since additional medications can affect BMD, there is uncontrolled heterogeneity among patients in each category, which was not completely analyzed in the multivariable study. Lastly, a few patients were omitted during the assessment process due to an FN or LS fracture, which could have affected investigative results. To summarize, more randomized controlled trials are required to determine how long a delay in denosumab administration raises the risk of fractures.

## Conclusion

The findings of this study suggest that clinicians may have some flexibility to prescribe denosumab, particularly in clinical circumstances such as the COVID-19 pandemic, but the time between injections should not exceed 9 months.

## Acknowledgments

The authors acknowledge the efforts of the Department of Information Management of National Yang Ming Chiao Tung University Hospital at Yilan for collecting clinical data and providing administrative supports.

## Disclosure

The authors report no conflicts of interest in this work.

## References

1. Lane NE. Epidemiology, etiology, and diagnosis of osteoporosis. *Am J Obstet Gynecol*. 2006;194(2 Suppl):S3–S11. doi:10.1016/j.ajog.2005.08.047
2. Jackson RD, Donepudi S, Mysiw WJ. Epidemiology of fracture risk in the women's health initiative. *Curr Osteoporos Rep*. 2008;6(4):155–161. doi:10.1007/s11914-008-0027-3
3. Jackson RD, Mysiw WJ. Insights into the epidemiology of postmenopausal osteoporosis: the women's health initiative. *Semin Reprod Med*. 2014;32(6):454–462. doi:10.1055/s-0034-1384629
4. Aspray TJ, Hill TR. Osteoporosis and the ageing skeleton. *Subcell Biochem*. 2019;91:453–476. doi:10.1007/978-981-13-3681-2\_16



5. Kaunitz AM, McClung MR, Feldman RG, Wysocki S. Postmenopausal osteoporosis: fracture risk and prevention. *J Fam Pract.* 2009;58(11Suppl Postmenopausal):S1–S6.
6. Bijelic R, Milicevic S, Balaban J. Risk factors for osteoporosis in postmenopausal women. *Med Arch.* 2017;71(1):25–28. doi:10.5455/medarch.2017.71.25-28
7. Black DM, Rosen CJ. Postmenopausal Osteoporosis. *N Engl J Med.* 2016;374(3):254–262. doi:10.1056/NEJMcp1513724
8. Fink HA, MacDonald R, Forte ML, et al. Long-term drug therapy and drug discontinuations and holidays for osteoporosis fracture prevention: a systematic review. *Ann Intern Med.* 2019;171(1):37–50. doi:10.7326/M19-0533
9. Zhou J, Ma X, Wang T, Zhai S. Comparative efficacy of bisphosphonates in short-term fracture prevention for primary osteoporosis: a systematic review with network meta-analyses. *Osteoporos Int.* 2016;27(11):3289–3300. doi:10.1007/s00198-016-3654-z
10. Yu EW, Tsourdi E, Clarke BL, Bauer DC, Drake MT. Osteoporosis management in the era of COVID-19. *J Bone Miner Res.* 2020;35(6):1009–1013. doi:10.1002/jbmr.4049
11. Girgis CM, Clifton-Bligh RJ. Osteoporosis in the age of COVID-19. *Osteoporos Int.* 2020;31(7):1189–1191. doi:10.1007/s00198-020-05413-0
12. Deeks ED. Denosumab: a review in postmenopausal osteoporosis. *Drugs Aging.* 2018;35(2):163–173. doi:10.1007/s40266-018-0525-7
13. Bone HG, Wagman RB, Brandi ML, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the Phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol.* 2017;5(7):513–523. doi:10.1016/S2213-8587(17)30138-9
14. Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: different mechanisms of action and effects. *Bone.* 2011;48(4):677–692. doi:10.1016/j.bone.2010.11.020
15. Lamy O, Stoll D, Aubry-Rozier B, Rodriguez EG. Stopping denosumab. *Curr Osteoporos Rep.* 2019;17(1):8–15. doi:10.1007/s11914-019-00502-4
16. Khosla S, Hofbauer LC. Osteoporosis treatment: recent developments and ongoing challenges. *Lancet Diabetes Endocrinol.* 2017;5(11):898–907. doi:10.1016/S2213-8587(17)30188-2
17. Imaz I, Zegarra P, González-Enriquez J, Rubio B, Alcazar R, Amate JM. Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: systematic review and meta-analysis. *Osteoporos Int.* 2010;21(11):1943–1951. doi:10.1007/s00198-009-1134-4
18. Soong YK, Tsai KS, Huang HY, et al. Risk of refracture associated with compliance and persistence with bisphosphonate therapy in Taiwan. *Osteoporos Int.* 2013;24(2):511–521. doi:10.1007/s00198-012-1984-z
19. Fardellone P, Lello S, Cano A, et al. Real-world adherence and persistence with bisphosphonate therapy in postmenopausal women: a systematic review. *Clin Ther.* 2019;41(8):1576–1588. doi:10.1016/j.clinthera.2019.05.001
20. Hadji P, Papaioannou N, Gielen E, et al. Persistence, adherence, and medication-taking behavior in women with postmenopausal osteoporosis receiving denosumab in routine practice in Germany, Austria, Greece, and Belgium: 12-month results from a European non-interventional study. *Osteoporos Int.* 2015;26(10):2479–2489. doi:10.1007/s00198-015-3164-4

## Patient Preference and Adherence

Dovepress

### Publish your work in this journal

Patient Preference and Adherence is an international, peer-reviewed, open access journal that focusing on the growing importance of patient preference and adherence throughout the therapeutic continuum. Patient satisfaction, acceptability, quality of life, compliance, persistence and their role in developing new therapeutic modalities and compounds to optimize clinical outcomes for existing disease

states are major areas of interest for the journal. This journal has been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/patient-preference-and-adherence-journal>