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Letter to the Editor

Denosumab in Osteoporosis: Predicting Long-Term Efficacy beyond 10 Years

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Osteoporosis, characterized by diminished bone density and microarchitectural deterioration, has become a global health concern and can lead to increased fracture susceptibility and subsequent morbidity and mortality.[1] The goal of treating postmenopausal osteoporosis is to increase bone density and prevent fractures, and various medications have been developed to achieve these goals.[2,3] Denosumab, a fully human monoclonal antibody targeting receptor activator of nuclear factor-κB ligand (RANKL), has emerged as a key therapeutic tool for osteoporosis management.[4] Denosumab is a RANKL-mediated osteoclast differentiation inhibitor that strongly inhibits bone resorption, thereby reducing bone loss and lowering fracture incidence, making it a potent treatment for patients at high risk of fractures.[4,5] Many clinical trials and real-world studies have demonstrated denosumab's efficacy in improving bone mineral density (BMD) and mitigating fracture risk.[5,6] Therefore, denosumab is widely accepted by clinicians as an important treatment for osteoporosis management, as reflected in clinical guidelines.[2,7-11] Long-term studies of up to 10 years have demonstrated the continued effectiveness of denosumab in increasing bone density and preventing fractures.[5,12] Moreover, continuing treatment beyond the initial years confers further fracture risk mitigation, highlighting denosumab's sustained efficacy over prolonged durations.[5] Notably, a 10-year denosumab treatment yielded a substantial increase in spine (21.7%) and hip BMD (9.2%).[5]

Denosumab's potent inhibitory effect on bone resorption effectively reduces fracture risk and increases the likelihood of reaching target BMD compared to bisphosphonates.[13] Therefore, once fracture risk has been reduced to moderate after a period of denosumab treatment, the drug can be discontinued in favor of sequential treatment with bisphosphonates.[2] However, in some clinical situations, once denosumab treatment has been initiated, it may need to be continued. Some patients who have reached their goals wish to continue denosumab treatment because of high adherence, dosing convenience, and fewer side effects.[14] In patients who remain at high risk of fracture after 10 years of treatment,

continued treatment should be considered.[7] Denosumab discontinuation results in a rebound phenomenon and should be followed by an agent such as bisphosphonate.[15,16] However, in patients with advanced renal dysfunction, sequential therapy with bisphosphonates is not feasible, and there are difficult clinical situations where, once denosumab is administered, long-term therapy should be considered.

Denosumab was first administered to patients in South Korea in November 2016. Some patients will require long-term denosumab treatment (>10 years). However, there are currently no reports on the effect of denosumab treatment on BMD after a 10-year administration. Therefore, we used a statistical approach to predict the changes in BMD after 10 years of denosumab treatment. In this study, we analyzed the results of the original Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) extension study and clinical studies to make statistical projections of the effects of denosumab treatment after 10 years. Utilizing multiscale indirect response models based on pharmacological studies is an appropriate approach to understanding the integrated dynamic impact of denosumab on longitudinal changes in BMD.[17-19] We utilized the following two methods as predictive models.

NON-LINEAR MODEL

This model transforms time (years) into a quadratic polynomial to incorporate non-linear (parabolic) patterns and is an appropriate analysis technique when data tend to increase or decrease over time or to rise or fall at specific points.[17,18] In the FREEDOM study, the lumbar spine was identified as having a pattern of continuous increase over time following denosumab administration,[5] so a non-linear model was used to predict lumbar spine changes. The formula for this is $y=ax^2+bx+c$, where x is the independent variable (time), y is the dependent variable (BMD), and a, b, and c are the parameters: Model parameter (estimates) after fitting the quadratic regression model. The lumbar spine BMD predictions from these analyses are shown in Figure 1. Lumbar spine BMD continued to increase after 10 years, with a final predicted increase of 27.8% at 20 years.

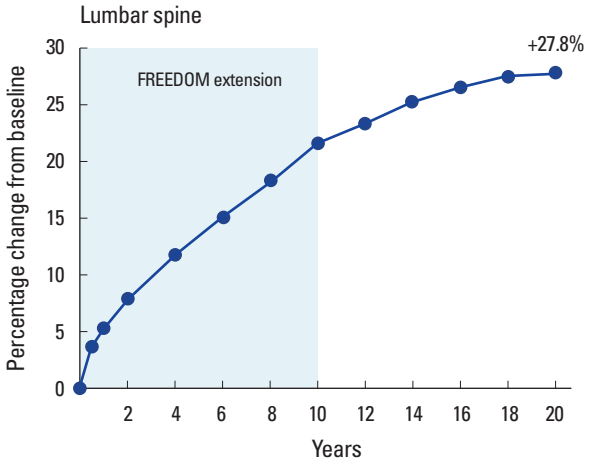

Fig. 1. Prediction of duration of denosumab treatment and percentage change from baseline in lumbar spine bone mineral density. FREEDOM, Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months.

LOGISTIC GROWTH MODEL

The logistic growth model is an appropriate modality for modeling S-shaped growth curves, often found in biological processes or phenomena and characterized by initial rapid growth, followed by a gradual slowdown in growth, and finally, stabilization as it approaches a maximum value.[19] Total hip BMD tended to slow down after a period of denosumab administration in previous studies [5,20]; therefore, the logistic growth model is a suitable model for predicting hip BMD. The formula used in this model is $BMD=\frac{k}{1+e^{-r(t-t_0)}}$, where each variable represents the following: (1) BMD: BMD value at the time (t) you want to predict; (2) k: The maximum level of BMD that can be reached, set to a value slightly larger than 1.2 times the maximum value of the 10-year BMD; (3) r: Growth rate, where higher values indicate faster growth, typically ranging from 0.01 to 1 in biological data, set to 0.5; (4) t0: The time that represents the center of the growth curve, set to 5. The methodology of the logistic growth model is consistent with the principles outlined in the reference study, Appendix, Appendix Table 10, and Appendix Table 12, and the appendix of the FREEDOM trial provides additional details and context for the methodology used in this analysis.[5] The results of this analysis are shown in Figure 2. Total hip BMD was predicted to increase by 9.8% from baseline over 20 years, with a pattern of relatively modest BMD gains over

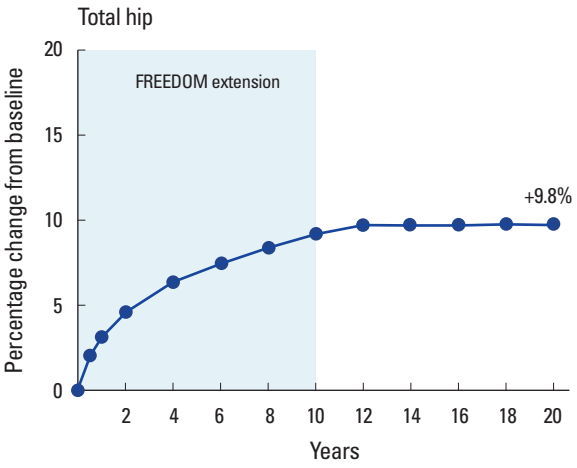

Fig. 2. Prediction of duration of denosumab treatment and percentage change from baseline in total hip bone mineral density. FREEDOM, Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months.

10 years that were maintained for 20 years. The attenuation observed may be attributed to the impact of denosumab on bone remodeling units (BMUs). Denosumab inhibits BMU activity, leading to a reduced bone turnover rate and consequently, a slower increase in BMD over time. The study by Bone et al. [5] demonstrated that after five years of denosumab treatment, the mean degree of mineralization reaches a peak, suggesting a potential deceleration in BMD gains with prolonged treatment. Additionally, the pharmacokinetics and finite element modeling research by Hambli et al. [21] indicated an initial rapid rise of approximately 3% in BMD at the femoral neck, total hip, and trochanter regions during the first year of treatment, followed by a more gradual increase thereafter.

Denosumab has become an essential treatment for osteoporosis, and many postmenopausal patients with osteoporosis receive denosumab to increase bone density and prevent fractures. The effectiveness of denosumab for up to 10 years has been well-documented; however, there have been no reports of outcomes beyond that time. Statistical analyses were used to predict BMD changes after 10 years of denosumab treatment. However, this is an arithmetic and statistical prediction that does not consider clinical parameters and the effects of denosumab on bone physiology. Real-world evidence from clinical settings is required to provide a clearer rationale. Until more definitive evidence is available, clinicians may consider our findings as only part of the evidence base for guidance in patients taking denosumab for 10 years or more.

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Conflict of interest

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