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# Response to: Letter to the Editor From Fitzpatrick et al: “Zoledronate After Denosumab Discontinuation: Is Repeated Administrations More Effective Than Single Infusion?”

**verso running head:** *The Journal of Clinical Endocrinology & Metabolism*, 2024, Vol. XX, No. XX

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We thank Dr. Fitzpatrick, Dr. Lannon and Dr. McCarroll for their interest in our work.

The authors raised concerns about the 9.6% all-fractures rate after denosumab (Dmab) discontinuation in our cohort, whereas the multiple vertebral fractures (mVFX) rate was 1.9% ( 1, 2). In the FREEDOM Extension post hoc analyses, only mVFX has been associated with the “rebound,” as the incidence was higher in the group discontinuing Dmab after >3 years as compared with Dmab < 3 years and the placebo group; therefore, when exploring the efficacy of the sequential bisphosphonates (BPs) administration, it appears more appropriate to focus on mVFX ( 3). In a previous study we found an alarming mVFX rate of 21.2% in subjects discontinuing Dmab without sequential BPs and no mVFX in the group treated; in the present study, only 1 out of 53 patients (1.9%) had mVF, immediately before the first zoledronate (ZOL) [AQ2] was administered ( 4). So we should rather be “reassured” that the use of BPs in general and the repeated ZOL administration schedule suggested by the European Calcified Tissue Society are effective in reducing the rebound mVFX ( 5).

Likewise, although a treat-to-target approach has been called on when dealing with the Dmab discontinuation decision, the only evidence in the literature supporting such an approach refers to a gradual “in-treatment” reduction of nonvertebral fractures rate parallel to the T-score increase, which plateaus when reaching osteopenic values, so translating this concept when talking about a target to reach to safely discontinue Dmab could be debated, as it has not been demonstrated that such a target would reduce the following rebound mVFX incidence ( 6).

We agree that there is still work to do to improve the Dmab discontinuation management to avoid bone mineral density (BMD) loss. As already suggested by the European Calcified Tissue Society, more intensive bone turnover markers monitoring including 3 months of follow-up after the first ZOL and anticipated ZOL administration should be the first step ( 5), but let us take a step back. Our data shows that the BMD loss was significantly lower in the group treated with Dmab for ≤2.5 years and that the net BMD gain from the start of Dmab to the end of the follow-up after discontinuation was comparable in the groups with short, medium, and long Dmab duration ( 2). Such an observation, together with the fact that <3 years Dmab therapy is not associated with rebound mVFX, would be supportive of the use of Dmab for a short time in order to improve BMD more quickly and more safely ( 2). The idea of using short-term Dmab courses is reinforced by the data by Everts Graber et al, who reported that a single Dmab injection followed by a single ZOL administration led to a remarkable increase in BMD, comparable to that obtained with 2.5 years of Dmab ( 7).

As clinicians, we should not ignore the problem of the “rebound,” which is observed exclusively after >3 years Dmab therapy discontinuation, and it is time to think back on how to make the most of Dmab without exposing the patients to potential harm.

#### **Disclosures**[AQ3]

The authors have no conflict of interest to disclose.

#### **References**[AQ4]

- 1 **Fitzpatrick D, Lannon R, McCarroll K.** Letter to the editor from fitzpatrick et al: “zoledronate after denosumab discontinuation: is repeated administrations more effective than single infusion?”. *J Clin Endocrinol Metab.* 2024;dgae491.[AQ5]
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