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Letter to the Editor

Insufficient Mitigation of Bone Loss by Zoledronic Acid after Treatment with Denosumab

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TO THE EDITOR:

I read with great interest the article by Kadaru and Shibli-Rahhal [1] on the bone loss related to zoledronic acid (ZA) after denosumab treatment. They reported bone mineral density (BMD) changes in 12 patients who were treated with ZA after denosumab and found a significant decline in BMD at femoral neck. The authors have delivered a clinically important and interesting message.

Medical treatment for osteoporosis after cessation of denosumab is becoming more crucial. Modi et al. [2] reported that 48.8% and 64.3% out of 617 patients who were treated with denosumab discontinued treatment at 12 and 24 months, respectively. Other than in patients who have reached T-score of BMD over -2.5 by the denosumab treatment, the discontinuation might be either because of the difficulty in persistent treatment of osteoporosis which is asymptomatic before the osteoporotic fracture or because of the increased risk of atypical femoral fracture (AFF) or medication-related osteonecrosis of the jaw (MRONJ). The rebound effect after denosumab cessation involves the increase of the bone turnover markers (BTMs) and decrease of BMD.[3-6] One of the efforts to avoid the rebound effect was to start bisphosphonate treatment following denosumab discontinuation. Implementing bisphosphonate mitigated BMD loss in several observational studies,[3,7,8] one of which emphasized the beneficial effect of delayed administration of ZA.[7] The present study showed a decline in BMD after the switch of denosumab to ZA, and its independence to number of denosumab doses and the interval between the denosumab and ZA. Moreover, the described pathomechanism of incompetence of bisphosphonate after denosumab treatment due to absence of "open bone surfaces" seems plausible.

As stated in the limitations, the small number of included 12 patients is the biggest weakness of this study. The alleviation effect of ZA following denosumab might be underestimated in this study because of the small number of participants. Furthermore, there was no control group in this study where the patients did not receive any antiosteoporotic treatment after denosumab cessation. Leder et al. [9] found maintenance of BMD (-0.6 g/cm^2 in femoral neck, -0.8 g/cm^2 in total hip, and -1.2 g/cm^2 in spine) in 28 patients who were treated after the Denosumab and Teriparatide Administration (DATA) study compared to a significant loss of BMD in

those who were not treated (−4.2 g/cm^2 in femoral neck, −4.5 g/cm^2 in total hip and −10.0 g/cm^2 in spine). Interestingly, the authors suggest the loss in BMD is concentrated within 1 year of ZA and it may reach a plateau after a second dose. The number of patients who received second doses of ZA was only 5. It would have been difficult because of the small number of total included patients, but comparing the BMD changes between patients who had osteoporotic fractures and the others could give additional information. Even if the BMD or BTM levels aggravate after changing denosumab to ZA, if the risk of osteoporotic fracture does not increase, it may not be a clinically significant issue.

The absence of information on BTMs, serum vitamin D, and calcium levels at each time point is another limitation. The major finding of decrease of BMD when switching denosumab to ZA could be influenced by above factors. As implementation of potent antiresorptive treatment is mandated after denosumab cessation to avoid the rebound effect, evaluating the antiresorptive effect of following treatment is crucial. Previous studies found the decrease of BTMs by 26.2% (osteocalcin) to 35.2% (bone-specific alkaline phosphatase) with raloxifene,[10] and decrease of serum C-terminal telopeptide of type I collagen by 53.4% to 59.9% with ibandronate.[11] The suggested pathomechanism in the discussion might be also supported by such data. Despite their rarity, the potential risks of AFF and MRONJ are present with both bisphosphonate and denosumab.[12] Nonetheless, there was no information on the complications of using both medications. Comparison with the patients who were treated with anabolic agents such as parathyroid hormones or romosozumab after denosumab therapy could also be informative.

The paper clearly add to the significance of rebound effect of discontinuing denosumab. The authors also provide meaningful outcomes where ZA mitigates the loss of BMD but not sufficiently. For more accurate analysis, however, larger number of study patients and inclusion of laboratory data are needed to support this finding and the assumption that the main loss of BMD occurs within 1 year of ZA injection. Whether the decrease of BMD after shifting denosumab to ZA increases the risk of osteoporotic fractures is not addressed in the article but may be clinically significant.

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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