Response to Letter: Severe Rebound-Associated Vertebral Fractures After Denosumab Discontinuation

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We thank Dr. Rao and colleagues for their comments. We reply point by point.

First, the number of published figures and/or images depends on the editorial policy and the demands of the reviewers. For each patient, images of fractures or reports of radiologists are available on request.

Second, we agree that the transiliac bone biopsy is better than the vertebral biopsy to assess the status of bone structure and remodeling. As reported in the article, all of these women were referred at our center several months after the occurrence of vertebral fractures (VFs).

Third, discontinuation of denosumab results in bone turnover marker (BTM) rebound, which remains elevated 30 months after the last dose. It is therefore not possible, on the basis of elevated BTM, to distinguish patients with (9 to 16 months after the last dose) and those without VFs during this period.

Fourth, we agree that the BTM rebound is one part of the explanation for the risk of VFs. For the moment, BMT rebound is the best marker and the best explanation for several reasons. First, women who discontinued denosumab after 10 years had a severe bone mineral density decrease that reached levels lower than baseline: 10-year denosumab gain of 8.2% ± 1.7%; 1-year off treatment loss of −12.5% ± 1.4%; net loss of −5.4% ± 1.8% (1). Second, very few pathologies are associated with such elevation of BTM. Third, the number of VFs per patient is abnormally high to be explained only by the lumbar bone mineral density or the fracture risk assessment tool estimate. Fourth, the increased risk of VFs after vertebroplasty is unusually high.

Whatever the case and regardless of the mechanisms involved, the facts are there. It was urgent to inform. This was the role of our article. Since then, the risk of VFs after denosumab discontinuation has been recognized. The risk of VFs after denosumab discontinuation in the pivotal study Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months was presented at the 2016 American Society for Bone and Mineral Research Congress (2). Among subjects who sustained new VFs, there was a greater incidence of multiple new VFs in the denosumab (34/56, 60.7%) as in the placebo (10/29, 34.5%) group. Otherwise, the Swiss Agency for Therapeutic Products recognized the link between denosumab discontinuation and increased risk of multiple VFs in December 2016 (http://www.swissmedic.ch/index.html?lang=en.).

We agree that it is urgent to be able to better identify patients at risk for VFs after denosumab discontinuation. The biopsy of transiliac bone can help us to understand the mechanisms, but it is not easy to propose it in clinical routine.

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Abbreviations: BTM, bone turnover marker; VF, vertebral fracture.