



ELSEVIER

Contents lists available at [ScienceDirect](http://ScienceDirect.com)

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

Letter to Editor

Commentary to “Denosumab for bone health in prostate and breast cancer patients receiving endocrine therapy? A systematic review and a meta-analysis of randomized trials” (Galvano et al. J Bone Oncol 2019; 18:100252)

We read with great interest the systematic review and a meta-analysis of randomized trials on denosumab for bone health in cancer patients receiving endocrine therapy by Galvano A. et al. [1]. We disagree with the main conclusion of this review article, which is that denosumab administration can be considered effective and safe in this clinical situation.

In prostate cancer patients receiving androgen deprivation therapy, and in patients under adjuvant endocrine therapy for early-stage endocrine-sensitive breast cancer, denosumab is routinely discontinued when the hormonal treatment is interrupted, unless a diagnosis of osteoporosis persists. It is now well known that denosumab discontinuation is associated with a severe rebound effect that lasts 2 years, which combines an increase in bone turnover markers and a complete loss of the gained bone density [2]. This rebound effect is associated, in postmenopausal osteoporosis, with multiple spontaneous vertebral fractures (MSVF) as described in several case series and in the post-hoc follow-up of the pivotal FREEDOM trial [3–7]. Cases have also been described in men [8]. It is a severe secondary effect, as patients present a median of five (1–11) vertebral fractures 7–20 months (median 11) after the last denosumab injection [7]. 1–10% of women with postmenopausal osteoporosis discontinuing denosumab suffer of MSVF, and although bisphosphonates given at denosumab discontinuation probably decrease the MVSF risk, cases of fracture despite bisphosphonate treatment have been described [7].

One could think that patients receiving denosumab for bone health preservation during hormonal therapies designed for breast and prostate tumors with a low fracture risk might be protected from MVSF. No case has been described including patients with prostate tumors under hormonal treatment. However, unpublished data from the off-treatment follow-up of the ABCSG-18 trial suggests the risk is increased similarly to postmenopausal women in those treated with aromatase-inhibitors [9]: in this study, the hazard ratio for MSFV was 3.52 (CI 0.98, 12.64) in women who stopped denosumab as compared to women who stopped placebo. Indeed, we just published data on a cohort of 15 women with early-stage breast cancer treated with aromatase inhibitors and denosumab for bone loss prevention [10]: they suffered 1–11 (mean 4.0 ± 1.9) clinical vertebral fractures within 7–16 months after last denosumab injection. Importantly, these fractures appeared earlier in patients without osteoporosis before denosumab (9.4 ± 2.0 vs. 13.0 ± 2.0 months; $p = 0.005$), suggesting low fracture risk does not protect from this adverse event.

We are aware that there is no published data on denosumab discontinuation in the targeted population to be included in the meta-analysis. However, this risk should be discussed, and the absence of off-denosumab solid data cited as an important limitation of the study, as the safety profile should also consider the significant post-treatment events.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

- [1] A. Galvano, D. Scaturro, G. Badalamenti, et al., Denosumab for bone health in prostate and breast cancer patients receiving endocrine therapy? A systematic review and a meta-analysis of randomized trials, *J Bone Oncol* 18 (2019) 100252.
- [2] H.G. Bone, M.A. Bolognese, C.K. Yuen, et al., Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass, *J Clin Endocrinol Metab* 96 (2011) 972–980.
- [3] A.D. Anastasilakis, S.A. Polyzos, P. Makras, et al., Clinical features of 24 patients with rebound-associated vertebral fractures after denosumab discontinuation: systematic review and additional cases, *J Bone Miner Res* 32 (2017) 1291–1296.
- [4] B. Aubry-Rozier, E. Gonzalez-Rodriguez, D. Stoll, et al., Severe spontaneous vertebral fractures after denosumab discontinuation: three case reports, *Osteoporos Int* 27 (2016) 1923–1925.
- [5] S.R. Cummings, S. Ferrari, R. Eastell, et al., Vertebral fractures after discontinuation of denosumab: a post hoc analysis of the randomized placebo-controlled FREEDOM trial and its extension, *J Bone Miner Res* 33 (2018) 190–198.
- [6] E. Fernandez Fernandez, D. Benavent Nunez, G. Bonilla Hernan, et al., Multiple vertebral fractures following discontinuation of denosumab treatment: ten clinical cases report, *Reumatol Clin* (2019).
- [7] O. Lamy, D. Stoll, B. Aubry-Rozier, et al., Stopping denosumab, *Curr Osteoporos Rep* 17 (2019) 8–15.
- [8] P. Anagnostis, S.A. Paschou, E. Gonzalez-Rodriguez, et al., Spontaneous vertebral fractures in males with osteoporosis after denosumab discontinuation: a report of two cases, *J Clin Rheumatol* (2019).
- [9] G. Pfeiler, G.G. Steger, D. Egle, et al., Fracture risk after stopping adjuvant denosumab in hormone receptor positive breast cancer patients on aromatase inhibitor therapy – an analysis of 3,425 postmenopausal patients in the phase III ABCSG-18 trial. in *American Society for Bone and Mineral Research*. Montreal, Canada, *J Bone Miner Res* 32 (Suppl 1) (2018).
- [10] E. Gonzalez-Rodriguez, B. Aubry-Rozier, D. Stoll, et al., Sixty spontaneous vertebral fractures after denosumab discontinuation in 15 women with early-stage breast cancer under aromatase inhibitors, *Breast Cancer Res Treat* (2019).

<https://doi.org/10.1016/j.jbo.2020.100294>

Elena Gonzalez-Rodriguez^{a,1,*}, Bérengère Aubry-Rozier^a,
Delphine Stoll^a, Khalil Zaman^{b,3}, Olivier Lamy^{a,c,2}

^a Center of Bone Diseases, Lausanne University Hospital and University of
Lausanne, Lausanne, Switzerland

^b Breast Center, Lausanne University Hospital and University of Lausanne,

Lausanne, Switzerland
^c Service of Internal Medicine, Lausanne University Hospital and University
of Lausanne, Lausanne, Switzerland

E-mail address:

elena.gonzalez-rodriguez@chuv.ch (E. Gonzalez-Rodriguez).

* Corresponding author at: Center of Bone Diseases, Rheumatology Service, CHUV, Lausanne University Hospital, Rue Pierre-Decker 4, Lausanne CH-1011, Switzerland.

¹ ORCID ID 0000-0001-6512-6008.

² ORCID ID 0000-0003-3684-2376.

³ ORCID ID 0000-0002-2997-527X.