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LETTER TO THE EDITOR

Drug holidays in osteoporosis treatment: mind the gaps!

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Nayak et al. in their recent study [1] performed a meta-analysis of the literature regarding the effect of bisphosphonate discontinuation ("drug holiday") on bone mineral density (BMD) and fracture risk.

Some comments might be of interest. The authors synthesized evidence from both randomized controlled trials (RCTs) and retrospective cohorts. The results of the former with regard to fracture risk are in accordance with another systematic review, released as a position statement by the European Menopause and Andropause Society (EMAS) in 2017 [2]. In fact, four RCTs (fracture intervention trial long-term extension (FLEX) study [3], the Alendronate phase III osteoporosis treatment study [4] and the Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly-Pivotal Fracture Trial (HORIZON-PFT) extension studies [5, 6]) have been conducted on the purpose of anti-fracture efficacy of alendronate and zoledronic acid administration beyond 5 and 3 years of continuous use, respectively. The other RCTs included in the Nayak et al. meta-analysis [1] are interim and post hoc analyses of these hallmark studies and do not confer further evidence. Additionally, there are data from other prospective studies, and RCTs included in the EMAS paper, showing further increase in BMD and decrease in bone turnover with bisphosphonate (alendronate) continuation to 2–5 years. The BMD gain was generally maintained above pre-treatment levels after discontinuation (2–5 years) [2].

It must be underlined that there is also evidence for risedronate, the discontinuation of which for 1 year, after completion of a 3-year continuous regimen, seems to be safe in maintaining its anti-fracture efficacy and preserving BMD above the pre-treatment values. As this bisphosphonate has the lowest retention to bone compared with alendronate and zoledronic acid, a more frequent monitoring is recommended [2].

Another point is that the four retrospective studies included in the Nayak et al. [1] meta-analysis are highly heterogeneous regarding their design, age groups, adherence to bisphosphonate, as well as duration and cessation of treatment (I^2 value 74% and 94% for hip and any clinical osteoporotic fracture, respectively). As random effects model does not alleviate the heterogeneity issue, the pooled estimate for this meta-analysis is unlikely to be meaningful. Thus, the null effect on fracture risk as presented by the authors should be interpreted with caution and cannot be generalized for the whole osteoporotic population.

Since evidence for a beneficial effect of a "drug holiday" on reducing the risk of atypical femoral fractures and osteonecrosis of the jaw is weak (only one study [7]) and the sample size of the aforementioned RCTs is relatively small, clinicians should carefully individualize their decisions on bisphosphonate discontinuation. The latter seems to be safe only for patients at low fracture risk after 5 years of alendronate and 3 years of zoledronic acid or risedronate continuous use, such as those with femoral neck T score > -2.5 and no prevalent fracture [2].

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Compliance with ethical standards

Conflict of interest None.

References

1. Nayak S, Greenspan SL (2019) A systematic review and meta-analysis of the effect of bisphosphonate drug holidays on bone mineral density and osteoporotic fracture risk. Osteoporos Int 30:705–720. https://doi.org/10.1007/s00198-018-4791-3
2. Anagnostis P, Paschou SA, Mintziori G, Ceausu I, Depypere H, Lambrinoudaki I, Mueck A, Pérez-López FR, Rees M, Senturk LM, Simoncini T, Stevenson JC, Stute P, Trémollieres FA, Goulis DG (2017) Drug holidays from bisphosphonates and denosumab in postmenopausal osteoporosis: EMAS position statement. Maturitas 101:23–30
3. Black D, Schwartz A, Ensrud K et al (2006) Effects of continuing or stopping alendronate after 5 years of treatment: the fracture intervention trial long-term extension (FLEX): a randomized trial. JAMA 296:2927–2938
4. Bone H, Hosking D, Devogelaer J et al (2004) Alendronate phase III osteoporosis treatment study group (2004) ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 350:1189–1199
5. Black D, Reid I, Boonen S et al (2012) The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-pivotal fracture trial (PFT). J Bone Miner Res 27:243–254
6. Black D, Reid I, Cauley J et al (2015) The effect of 6 versus 9 years of zoledronic acid treatment in osteoporosis: a randomized second extension to the HORIZON-pivotal fracture trial (PFT). J Bone Miner Res 30:934–944
7. Schilcher J, Koeppen V, Aspenberg P, Michaelsson K (2014) Risk of atypical femoral fracture during and after bisphosphonate use. N Engl J Med 371:974–976