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Invited Editorial

"Holidays" for osteoporosis drugs: A case-based approach

HIGHLIGHTS

- A "drug holiday" can be considered for patients at low fracture risk
- It is optimal after completion of five years of alendronate and three years of zoledronic acid or risedronate use
- The "drug holiday" strategy should not be implemented for denosumab, estrogen, SERMs or teriparatide.

Keywords:
Osteoporosis
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Bisphosphonates
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Bisphosphonates are the most widely used anti-resorptive drug category and have established efficacy in reducing the risk of vertebral, non-vertebral and hip fracture [1]. However, their long-term use has been associated with an increased risk of adverse effects, including atypical femoral fractures (AFF) and osteonecrosis of the jaw (ONJ) [1]. These two adverse effects do not attenuate the bisphosphonates' anti-fracture efficacy, since their absolute risk is very low. The incidence of AFF (defined as atraumatic or low-trauma femoral fractures, located in the subtrochanteric or diaphyseal region) ranges from 3.2 to 50 cases per 100,000 person-years [2]; the risk increases with the duration of bisphosphonate use (>2-fold with >5 years of exposure) [2]. Nevertheless, for each AFF, >1200 fractures are prevented, including 135 hip fractures [2]. ONJ is mostly described in patients on high-dose intravenous bisphosphonates or with a personal history of cancer (the incidence is 1–15% in these subpopulations). ONJ has rarely been reported in purely osteoporotic populations (prevalence 0.001–0.04%, which increases with the duration of bisphosphonate use) [1].

The idea of a temporary discontinuation of bisphosphonates (a "drug holiday") has been developed to mitigate these two rare adverse effects. Another argument for this strategy is the long residence of bisphosphonates in the skeleton and the residual anti-fracture efficacy after their discontinuation [3]. Regarding the former argument, the only relevant study included 59 AFF cases and 263 controls (defined as those sustained a conventional subtrochanteric or diaphyseal fracture). After bisphosphonate withdrawal, the risk of AFF was reduced by 72% per year after last use [odds ratio (OR) 0.28, 95% confidence interval (CI) 0.21–0.38] [4].

What matters most is whether a "drug holiday" strategy can offset the gain in bone mineral density (BMD) and fracture risk reduction obtained by bisphosphonate use. Put differently, does prolonged treatment with bisphosphonates (without a "drug holiday") result in additional reductions in fracture risk?

Data from randomized controlled trials (RCTs) exist for alendronate ($n = 2$) and zoledronic acid ($n = 2$). Briefly, extension of alendronate treatment to ten years (after completion of five years of continuous use) did not decrease the risk of morphometric vertebral and non-vertebral fractures, whereas it did decrease the risk of clinical vertebral fractures by 55% [relative risk (RR) 0.45, 95% CI 0.24–0.85] [3]. With respect to zoledronate, extension to six years (after three annual infusions) reduced the risk for new morphometric vertebral fractures by 49% (OR 0.51, 95% CI 0.26–0.95), without any effect on clinical vertebral and non-vertebral fracture risk. Moreover, extension to nine years conferred no further benefit at any skeletal site [3]. Regarding risedronate, one RCT showed that anti-fracture efficacy was maintained, at least for one year (after three years of treatment) [3]. In all these trials, BMD and concentrations of bone turnover markers were generally retained above pre-treatment values. Of note, no increase in AFF and ONJ was shown with prolonged bisphosphonate treatment [3].

A recent meta-analysis, including data from retrospective studies ($n = 4$), did not show any difference in the adjusted hazard ratio (HR) of hip or any clinical osteoporotic fracture between women who discontinued and those who extended bisphosphonate use (HR 1.09, 95% CI 0.87–1.37 and 1.13, 95% CI 0.75–1.70, respectively) [5]. However, the high heterogeneity in study design, age groups, adherence and duration of drug cessation reduce the external validity of these studies.

Post-hoc analyses support the notion that a "drug holiday" strategy is mostly appropriate for patients at low fracture risk (defined as femoral neck T-score > -2.5, age < 70 years, no prevalent fractures and absence of a disease or medication associated with increased fracture risk). The "holiday" can be considered after completion of five years of

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alendronate and three years of zoledronic acid or risedronate use [3]. The duration of the "holiday" and the frequency of BMD evaluation should be individualized, depending on the T-scores at the time of drug withdrawal and the patient's fracture risk. BMD should be assessed every 2–4 years in patients at low to moderate risk; therapy re-initiation should be considered for patients with bone loss or transition to high fracture risk category [6]. As risedronate has the lowest retention in bone compared with alendronate and zoledronic acid, closer monitoring is suggested [3].

The "drug holiday" strategy should not be implemented where other anti-osteoporotic agents are being used, such as denosumab, menopausal hormone therapy (MHT), estrogen-receptor modulators (SERMs) or teriparatide. Denosumab discontinuation has been associated with increased risk of rebound fractures in both males and females [3,7]; therefore, sequential therapy with another anti-osteoclastic agent (i.e. bisphosphonates) is suggested [8]. Available data (from small non-randomized trials) show a protective effect for zoledronic acid and alendronate, regarding BMD retention and fracture risk prevention, following denosumab discontinuation [8]. The question of "when to stop denosumab" cannot be answered safely. However, a very recent study, analyzing data from the Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) trial, showed a plateau in non-vertebral anti-fracture efficacy after completion of ten years of continuous denosumab use (n = 1343) and achievement of total hip T-scores between -2 and -1.5. This association was independent of age and prevalent vertebral fractures [9]. Thus, the idea of a "treat to target" approach in osteoporosis treatment has just emerged.

The best sequential anti-osteoporosis treatment is still a matter of debate, but an anti-resorptive agent should be considered after completion of teriparatide or abaloparatide treatment due to the rapid bone loss after their discontinuation [6]. This is also the case for MHT and SERMs [6]. Since no comparative data from RCTs exist on this concept, a patient-centered approach taking into account the individual's fracture risk and the expected efficacy of the available options is suggested.

Contributors

Panagiotis Anagnostis designed the editorial and searched the literature, analyzed the data and wrote the first draft.

Stavroula A. Paschou was responsible for the text format and reviewed the manuscript.

Eustathios Kenanidis reviewed the manuscript and provided critical scientific input.

Irene Lambrinoudaki reviewed the manuscript and provided critical scientific input.

Michael Potoupnis reviewed the manuscript and provided critical scientific input.

Eleftherios Tsiridis reviewed the manuscript and provided critical scientific input.

Dimitrios G. Goulis provided critical scientific input and had the primary responsibility for the editorial's final content.

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Panagiotis Anagnostis
Unit of Reproductive Endocrinology, First Department of Obstetrics and Gynaecology, Medical School, Aristotle University of Thessaloniki, Greece
Center of Orthopaedic and Regenerative Medicine Research (CORE), Centre for Interdisciplinary Research and Innovation (CIRI), Aristotle University of Thessaloniki, Thessaloniki, Greece
Academic Orthopaedic Unit, Aristotle University Medical School, General Hospital Papageorgiou, Thessaloniki, Greece
Corresponding author at: Unit of Reproductive Endocrinology, First Department of Obstetrics and Gynaecology, Medical School, Aristotle University of Thessaloniki, "Papageorgiou" General Hospital, 56403, Nea Efkarpia, Thessaloniki, Greece.
E-mail address: pan.anagnostis@gmal.com

Stavroula A. Paschou
Second Department of Obstetrics and Gynaecology, Medical School, National and Kapodistrian University of Athens, Greece

Eustathios Kenanidis
Center of Orthopaedic and Regenerative Medicine Research (CORE), Centre for Interdisciplinary Research and Innovation (CIRI), Aristotle University of Thessaloniki, Thessaloniki, Greece
Academic Orthopaedic Unit, Aristotle University Medical School, General Hospital Papageorgiou, Thessaloniki, Greece

Irene Lambrinoudaki
Second Department of Obstetrics and Gynaecology, Medical School, National and Kapodistrian University of Athens, Greece

Michael Potoupnis
Center of Orthopaedic and Regenerative Medicine Research (CORE), Centre for Interdisciplinary Research and Innovation (CIRI), Aristotle University of Thessaloniki, Thessaloniki, Greece

Academic Orthopaedic Unit, Aristotle University Medical School, General Hospital Papageorgiou, Thessaloniki, Greece

Eleftherios Tsiridis
Center of Orthopaedic and Regenerative Medicine Research (CORE), Centre for Interdisciplinary Research and Innovation (CIRI), Aristotle University of Thessaloniki, Thessaloniki, Greece
Academic Orthopaedic Unit, Aristotle University Medical School, General Hospital Papageorgiou, Thessaloniki, Greece

Dimitrios G. Goulis
Unit of Reproductive Endocrinology, First Department of Obstetrics and Gynaecology, Medical School, Aristotle University of Thessaloniki, Greece
Center of Orthopaedic and Regenerative Medicine Research (CORE), Centre for Interdisciplinary Research and Innovation (CIRI), Aristotle University of Thessaloniki, Thessaloniki, Greece

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