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Review

Therapeutic holidays in osteoporosis: Long-term strategy of treatment with bisphosphonates☆

María Jesús Moro Álvarez[a,*], José Luis Neyro[b], Santos Castañeda[c]

[a] Servicio de Medicina Interna, Hospital Universitario Infanta Leonor, Madrid, Spain
[b] Servicio de Ginecología y Obstetricia, Hospital Universitario Cruces, Baracaldo, Vizcaya, Spain
[c] Servicio de Reumatología, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria La Princesa, Madrid, Spain

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ABSTRACT

Oral bisphosphonates (BFs) are drugs widely used in the treatment of osteoporosis and placed as first-line treatment for osteoporosis in most clinical guidelines. BFs are effective drugs that reduce the incidence of fractures and even reduce mortality. Because of their great affinity for bone, BFs have shown that even when they are discontinued still offer a latent protective effect on bone mineral density, maintaining their anti-fracture effect.

However, prolonged use for years has been linked to the gradual emergence of complications such as osteonecrosis of the jaw or atypical femur fractures, which have raised questions as when to hold and when to make a final or temporary break, recognized as periods of rest or "therapeutic holidays" of these drugs.

Thus, in patients treated with BF for a period of 3–5 years with a low risk of fracture, the drug should be discontinued and restarted when there is an indication for treatment. In contrast, in patients with moderate risk, therapeutic holidays are advised, while reassessing after 2–3 years for restarting purposes. Finally, in patients with high risk of fracture, treatment with BF should not be withdrawn.

Vacaciones terapéuticas en osteoporosis: estrategia en el tratamiento a largo plazo con bifosfonatos

Palabras clave:
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RESUMEN

Los bifosfonatos (BF) orales son fármacos ampliamente utilizados en el tratamiento de la osteoporosis y se sitúan como primera línea de tratamiento para la osteoporosis en la mayoría de las guías clínicas. Son fármacos eficaces que reducen la aparición de fracturas e incluso disminuyen la mortalidad. Debido a su gran afinidad por el tejido óseo, los BF han demostrado que, incluso cuando se interrumpe su administración, siguen ofreciendo un efecto protector sobre la densidad mineral ósea e incluso sobre la aparición de nuevas fracturas.

Sin embargo, su uso prolongado durante años se ha relacionado con la aparición de algunas complicaciones, como la osteonecrosis mandibular o las fracturas atípicas de fémur, que han cuestionado la duración del tratamiento con estos fármacos y abierto la posibilidad de realizar interrupciones, definitivas o temporales, reconocidas como «vacaciones terapéuticas».

Así, en pacientes tratados con BF durante un período de 3 a 5 años con riesgo bajo de fractura, se aconseja retirar el fármaco y reiniciarlo cuando vuelva a presentar indicación de tratamiento. En cambio, en pacientes con riesgo moderado, se aconseja realizar vacaciones terapéuticas y reevaluar a los 2-3 años para reiniciar el tratamiento. Por el contrario, en aquellos pacientes con riesgo elevado de fractura no debería retirarse el tratamiento.

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* Corresponding author.
E-mail address: mariajesus.moro@salud.madrid.org (M.J. Moro Álvarez).

Introduction

Osteoporosis is a chronic disease, like other diseases such as hypertension or diabetes mellitus, requires indefinite treatment. This does not mean that drug administration must necessarily be permanent or that the administered drug should always be the same, and, of course, treatment discontinuation will always be justified when the risk/benefit ratio becomes unfavourable.

This scenario arises in the following situations: when the therapeutic goals are reached, when there is loss of efficacy or when the risk of developing side effects increases.

The objectives to be achieved in the treatment of osteoporosis are not well defined and they need to be individualized depending primarily on the patient's fracture risk at any time during the evaluation. In general, we can distinguish three different scenarios:

(1) When there is no previous fracture: the therapeutic objective can be set to −2.5 T-*score* in the femoral neck, so that when this value is reached, the treatment could be withdrawn.
(2) When there is a previous fracture which occurred before the last 3–5 years (in fact, probably, before starting the treatment): the densitometric goal should be a little more demanding: −2.0 T-*score*. Reached this value, treatment may be temporarily suspended.
(3) If a previous fracture has occurred in the last 3–5 years (when the patient was probably already in treatment), the patient should continue treatment regardless of the bone mineral density (BMD) value.

The objectives achieved tend to disappear quickly after treatment discontinuation (resumption of bone loss), so a definitive treatment withdrawal is hardly warranted. So, with osteoforming (teriparatide), antiresorptive (raloxifene, bazedoxifene, denosumab) treatments and dual mechanism drugs (strontium ranelate), discontinuation of treatment results in a gradual loss of the beneficial effect achieved and in the progressive loss of BMD. Bisphosphonates (BPs) are the only exception to this fact.

BP's bone affinity provides a osteoprotective "lingering effect" on BMD and even on the onset of the antifracture effect after being discontinued, as demonstrated in the study *Fracture intervention trial Long-term EXtension* (FLEX).[1]

Is safety being as important as its efficacy. Besides being effective in the treatment of osteoporosis, BP drugs have an excellent safety profile.[2–5] The fracture risk reduction with BP ranges between 40 and 70% for vertebral fracture and 40–50% for femur fracture. Besides, BPs have also shown a reduction in mortality. However, prolonged use may be associated with adverse effects that were not described in the main drug approval trials. According to the latest data, the risk of osteonecrosis of the jaw with oral BP is: OR 2.32 (95% CI 1.38–3.91).[6,7] Moreover, the absolute risk of atypical fractures of the femur (AFF) in patients treated with BP range from 3.2 to 50 cases per 100,000 people treated per year, and increases with prolonged exposure.[8–10]

Concept of therapeutic holidays

Strictly speaking, "therapeutic holidays" refer to the temporary interruption of osteoporosis treatment with BP (alendronate [ALN], risedronate [RSN], ibandronate [IBN] or zoledronate [ZLN]) with the intention of making its probable antiresorptive "persistent effect" last longer given the fixing effect these drugs have on bone tissue, while minimizing the possible occurrence of any of the complications associated with its use, which have shown to be more frequent the longer the treatment is. The term "holiday" implies that, at some later stage, the same drug will be reintroduced again.

The main purpose for which therapeutic holidays with BP arise is to maintain a proper balance between benefit (efficacy or effectiveness to prevent the occurrence of osteoporotic fractures) and the safety associated with the long term use of a particular BP for more than 3–5 years.

Of all the complications described with BP, the gradual emergence of AFF cases is what has alerted and questioned the long-term treatment with these drugs. From a pathophysiological point of view, it seems that long term treatment with BP leads to excessive suppression of bone remodelling, a situation resulting in greater mineralization, accumulation of aged bone without remodelling and, therefore, a higher risk of microfractures.[11] However, this has not been fully demonstrated in histological studies with patient series.[12,13]

Another reason to take into account in connection with implementing "therapeutic holidays" is undoubtedly the low adherence of patients to an indefinite treatment, although whether these scheduled interruptions increase compliance still needs to be demonstrated and, additionally, we cannot ignore the pharmaceutical cost.

However, this strategy is only acceptable for treatment with BP, and not for other drugs used in osteoporosis, such as denosumab, oestrogen receptor modulators, teriparatide, or strontium ranelate.

Pharmacokinetics of bisphosphonates

BPs, especially the aminated ones, such as ALN, RSN, IBN or ZLN, are potent antiresorptive agents which slow down resorption markers in an intense and sustained manner, even after several years,[14–16] while significantly increase BMD.[17]

Pre-clinical and experimental studies have shown that, after absorption, the BPs are deposited in the bone or rapidly eliminated in the urine, with minimal accumulation in non-calcified tissues. In the case of ALN, 50% of the drug will be retained in the skeleton, after a single dose, in the first week of treatment, while the other 50% will be excreted in the urine. Subsequently, retention is much slower and progressive, so that in the sixth month the skeletal retention amounts to 67%. Simultaneously, renal elimination is also slow and gradual, so that after several years, the drug is still being eliminated, estimating a terminal half-life of over 10 years.[18]

After fixation in the bone's hydroxyapatite and performing its antiresorptive effect, and as a result of the coupled bone formation, ALN is "embedded" in the bone matrix and remains there for a while, probably inactive.[19] Later, following a new activation on the remodelling units, part of the ALN embedded in the bone with high turnover is released again, becoming active and continuing with its antiresorptive effect. In fact, in ALN's Summary of Product Characteristics, it mentions that if the treatment is discontinued after 10 years (at a dose of 70 mg/wk), the estimated blood circulation skeletal release would be approximately the same as the one that would occur by oral administration at doses of 2.5 mg/day.[20]

Differences between bisphosphonate agents

Despite sharing a similar molecular structure (2 phosphate groups linked by a carbon atom), not all BPs are the same (Fig. 1). Although the R1 chain is constant across BPs (OH group) and is responsible for the affinity to bone hydroxyapatite, the R2 chain is variable and is responsible for the antiresorptive potency, that is, determines the ability to inhibit phosphoribosyl pyrophosphate synthetase of the osteoclast, essential enzyme to maintain the function and viability of this cell.[1,6,7,10]

Therefore, there are differences in both, affinity for bone tissue and antiresorptive potency between different BPs. For example, among the most used amino bisphosphonates in osteoporosis, IBN