DEAR EDITOR:
The wake-up call from the Food and Drug Administration (FDA), the European Medicines Association (EMA) and the Spanish Agency for Medicines and Health Products (AEMPS) regarding the relationship between the use of bisphosphonates (BP) and the incidence of atypical femoral fractures has caused people to start to consider the option of a break in the continuous use of BP, so-called “therapeutic holidays”. The American Society for Bone and Mineral Research (ASBMR) quickly initiated a working group which published a position statement on the theme of atypical fractures, above all to describe the criteria by which to define them1,2. Since then, there have been various authors who have reviewed the prevalence of atypical fractures in their records and their possible relationship with the use of BP3-5. The increased risk due to their continuous use appears to be clearly related to time, with the relative risk increasing substantially from the fourth year3, although the absolute risk is in the region of 11 fractures for each 10,000 years.

These data have led to a serious debate about how long a period BP should be administered and if therapeutic holidays might be opportune. To date, the most commonly accepted opinion seems to be not to allow these holidays in patients who remain at high risk of suffering a new fragility, while with the relative risk increasing substantially from the fourth year3, although the absolute risk is in the region of 11 fractures for each 10,000 years.

This could be described as a clinical case debate: therapeutic holidays, yes or no?

DEAR EDITOR:
I read with interest the special document publish recently in your review in which, on the one side  Drs Sosa Henríquez and Gómez de Tejada and on the other, Dr Malouf Sierra, debated the appropriateness or otherwise of therapeutic holidays for bisphosphonates, based on a clinical case1. The authors present a case of a woman of 63 years of age with a history of early menopause and vertebral fracture at 53, for which she had received treat-
ment with alendronic acid for 10 years with good tolerance and compliance. In a current densitometry the patient had a T-score of -2.5 in the lumbar spine and -1.5 in the femoral neck, which means a significant increase in bone mineral density in both areas relative to that at the start of the treatment. The authors told us that she had experienced no falls or fractures during this 10 years, and posed the question as to whether or not a therapeutic holiday for bisphosphonate should be given.

In any disease, before we consider whether to continue, change or withdraw a treatment, we should ascertain whether or not this treatment has worked during the period it has been used. In the case presented to us we are told that the patient had not suffered new fractures, but it appears that this refers to clinical fractures. To ensure that no morphometric vertebral fractures had occurred we would have to carry out a dorsal-lumbar X-ray or a vertebral morphometry. Only then would we be able to say that there were no fractures, given that a high percentage of vertebral fractures are asymptomatic.

So, once the presence of new morphometric vertebral fractures in the patient has also been discounted, I think that this more than justifies proposing therapeutic holidays for a drug which has a residual effect in the bone, meaning that it would continue to act in spite of not being administered, and which is not without well-known complications. Some of the arguments Drs Sosa and Gómez de Tejada use to defend the continuation of the treatment are debatable. For example, they compare the discontinuation of treatment with bisphosphonates with that of antibiotics or anti-inflammatory drugs, which have half-lives of only a few hours.

Sosa and Gómez de Tejada defend the maintenance of treatment with alendronate in the patient because, to their understanding, the patient continues to be a high risk patient simply for having suffered an earlier vertebral fracture. It is true that patients with a previous vertebral fracture have a higher risk of fracture than those without fracture, but this risk diminishes with time, and after 10 years without the appearance of new fractures the risk is already much lower, even more so if the fact that the patient has been receiving antiresorptive treatment with alendronate for all those years is taken into account. With bisphosphonates we achieve not only an increase in BMD, which is already associated with a reduction in the risk of fracture, but also an improvement in other bone parameters more related to quality, and which explains more than 80% of its anti-fracture effect.

Finally, the authors Sosa and Gómez de Tejada comment that the bisphosphonates are quite safe drugs, and this is completely true, given that the risk of serious complications such as osteonecrosis of the jaw or atypical fracture are extremely low in patients with osteoporosis treated with oral bisphosphonates. But to take this risk, low as it may be, is only justifiable in patients in whom the expected benefits of the drug are clearly greater than this risk, as could be the case in the patient just after the fracture, but not 10 years after. Furthermore, there is a clear association between these complications and the period of exposure to bisphosphonates.

It would be more difficult to decide on the discontinuation of bisphosphonate in the case of a patient with a T-score in the spine of < -3. As the T-score at the start of treatment was -3.7 and the patient had not had fractures during these 10 years, we could say that the alendronate had worked, but possibly the patient’s current risk remains sufficiently high that the risk of osteoporotic fracture clearly outweighs the risk of complications. This would justify maintaining the antiresorptive treatment with bisphosphonates or with another drug with better reversibility in the bone such as denosumab.

But returning to the case presented to us, I believe that it is more than reasonable to propose therapeutic holidays for bisphosphonates. This does not mean leaving the patient without any antifracture effect, since we know that their skeleton will “ooze” alendronate, neither should we forget their “too” antiresorptive effect just after the fracture, but not 10 years after. Furthermore, there is a clear association between these complications and the period of exposure to bisphosphonates.

So, once the presence of new morphometric vertebral fractures in the patient has also been discounted, I think that this more than justifies proposing therapeutic holidays for bisphosphonates.
from the CONDOR dental PBRN. J Dent Res 2011;90:439-44.


DEAR EDITOR:
The optimum duration of a treatment for osteoporosis is not defined, the exception being the use of teriparatide whose administration is limited to two years. We know that for other drugs it should be longer, but we do not understand well on what criteria this decision might be based. Undoubtedly, these criteria should include the persistence of the therapeutic indication, but other aspects should also be taken into account.
The debate published in this review1, based on a clinical case by, on the one side Dr Sosa et al. and on the other Dr Malouf, is very interesting. It deals with the question of whether or not to continue with bisphosphonate (BP) in a patient after 10 years of treatment.
In this work they analyse in depth the appearance of adverse effects in relation to the period of time for which the BP has been taken. On the one hand, the appearance of osteonecrosis of the jaw (ONJ), an infrequent complication whose risk does not justify the cessation of long-term treatment, and on the other, the appearance of atypical femoral fractures in these patients, a complication whose incidence could be related to the duration of use of these drugs.
The Spanish Agency for Medicine and Health Products (AEMPS), on April 15th 2011 published an information briefing in which it recommended that patients treated with BP be periodically evaluated (especially after the first 5 years). As Dr Sosa comments, many doctors have started to withdraw treatment with BP from their patients without evaluating whether this withdrawal was appropriate or not. In practice, this translates into leaving a large number of patients with a high risk of fracture without therapeutic protection. We know: firstly, that exposure to BPs increases the incidence of atypical femoral fracture; secondly, that this incidence increases with the duration of exposure to this drug; and thirdly, that in any case, in patients with osteoporosis the incidence of atypical femoral fracture is very low compared with that of osteoporotic fractures.
The consideration of the aforementioned works allow one to deduce that the decisive factor in deciding whether a treatment with BP should be continued or not, is the risk of osteoporotic fracture which the patient has at the time of proposing the discontinuation of the therapy. The risk is considered to be high when the patient has a bone mineral density (BMD) in the femoral neck lower than -2.5 T, or when they have a history of a previous osteoporotic (vertebral or hip) fracture. This therapeutic approach has become particularly clear from various recent works in the literature2-3 and is picked up in a recently published work in the review, the American Journal of Medicine4. Here the patients are classified in three categories: a) high risk (T-score in the hip lower than -2.5; previous vertebral or hip fracture; treatment with high doses of corticoids); b) moderate risk (T-score in the hip higher than -2.5; absence of previous hip or vertebral fractures); c) low risk (lack of therapeutic criteria at the start of treatment, meaning: treatment inappropriate from the start). In the first category the withdrawal of treatment is not considered to be justified, but with periodic re-evaluation of the therapeutic indications. In the second, the consideration of a temporary withdrawal (“therapeutic holiday”) is advised after 3-5 years of treatment. In the third category, logically, the treatment should be discontinued.
The Spanish Society for Bone and Mineral Metabolism Research (SEIOMM) includes these recommendations in a document which takes the aforementioned criteria, adding that if the withdrawal of treatment with BP is desired for some reason from a patient who still has the criteria for being at high risk of osteoporotic fracture, the therapeutic approach should not simply be to discontinue it but to substitute it with another therapeutic agent which acts in a different way5. In the clinical case with which we are concerned, the patient had, after 10 years of treatment, osteoporosis in the lumbar spine and a history of vertebral fracture, which means that they ought to be considered as a high risk patient, and that the treatment should be continued or changed for another treatment, since the incidence atypical fractures in patients who have had treatment with BP for more than 10 years is not known.

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DEAR EDITOR:
We have read with interest the clinical case debate regarding therapeutic holidays1, which clearly reflects the positions for and against the cessation of treatment with bisphosphonates after a period of 5-10 years for alendronate, and perhaps 3-6 years

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for zolendronate. We have less evidence in relation to risedronate and even less regarding the risks and benefits of maintaining treatment or not beyond 10 years\(^2\), as is raised by the case under debate. It is probable that much of the argument that lies behind this subject stems from the lack of incontestable evidence on how to proceed in a case like this, and can only be understood after the appearance of rare complications associated with chronic treatment with bisphosphonates – and other powerful anti-catabolics – such as osteonecrosis of the jaw or atypical fractures\(^3\).\(^4\). These possible complications have caused the medical equivalent of a “social panic”, although their risk is really low compared to the benefits, due to the efficacy of these drugs when used in patients with a real risk of osteoporotic fractures\(^5\).\(^6\).

Therefore, as stated in SEIOMM’s recommendation document\(^7\), the type of patient who most benefits from continuing the treatment beyond 5 years seems clear. However, we should not forget that among women treated for osteoporosis for 5 years with alendronate and monitored for a further 5 years without treatment, new fractures appear in 22% of cases and, more significant, the vast majority of these will appear during the first year that we have no markers to help us identify these patients\(^8\).

Although scarce, and methodologically questionable, this is the best evidence for treatment with bisphosphonates for up to 10 years. In any case, what is striking is the preoccupation the medical community has with this specific issue when compared with other therapies employed in other pathologies such as, for example, myopathy, diabetes, nephrotoxicity, cataracts, cognitive deterioration or erectile dysfunction, among others, associated rarely with statins (although its benefits in relation to overall and cardiovascular mortality continue to be clear)\(^9\). The same may be said of the proton pump inhibitors, with which have been associated pneumonia, \textit{clostridium difficile} infection, osteoporotic fractures, thrombocytopenia, iron, vitamin B12 and magnesium deficiency, rhabdomyolysis and interstitial nephritis, and which continue to be widely used drugs\(^10\).

What might happen in the risk-benefit balance in the treatment with bisphosphonates beyond 10 years is reminiscent of one of the best-known sequences in the film “Out of Africa” in which the protagonist, Karen Blixen, played by Meryl Streep, says: “When in the past explorers arrived at the limits of the known world they were afraid to continue and wrote” “There be dragons!”\(^11\). Until we have solid proof – and this seems unlikely – we can continue to discuss this \textit{ad infinitum}. Hopefully, at least, we will soon have alternative therapies which have been proven to be efficacious in this context, before, as it appears, for fear of dragons we stop treating even more patients at risk.

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**DEAR EDITOR:**

I have read the clinical case debate “Therapeutic holidays: yes or no?” published recently in this journal\(^1\) and, having recognised the excellent arguments and wide literature reviews of those putting the case for and against continuing treatment, dare I, as a doctor, give my opinion on the question raised?

Focusing on the case: it concerns a patient in whom treatment was initiated at 53 years of age due to a vertebral fracture and bone mineral density (BMD) in the range for osteoporosis. The risk factors were corrected and treatment initiated with alendronate and vitamin D, which seems to me a correct approach. This treatment has been maintained for 10 years and is now being assessed as to whether to continue with it or to take what is called a “therapeutic holiday”. In terms of the comment about the BMD in the hip not being in the range for osteoporosis, one should take into account that, at 53 years of age, bone loss occurs primarily in the spine. This means that studies to evaluate hip fractures are carried out in older populations, when this fracture starts to appear\(^2\). The situation of the 53 years old patient after 10 years of treatment with alendronate and vitamin D is the following: she has not suffered new fractures (the risk of fracture is greater in the year following the appearance of a fracture); her BMD has increased and she currently has a T-score of -2.5, having reached a plateau in the last two years; and
Lastly, the marker for bone resorption has reduced with treatment. Given the residual effects of the disphosphonates after their withdrawal\(^4\), and the fact that the bone markers may be elevated for 6 months, or even up to a year and a half, after treatment stops, depending on the type of disphosphonate used, in my opinion, this patient may discontinue the alendronate and stop the intake of the vitamin D necessary, since after 10 years there have been no new fractures and the BMD has increased to become stable in the last two years. On the other hand, I would suggest carrying out a new assessment after a year or a year and a half to see how it is developing and, depending on the clinical situation at that time, I would make an assessment as to whether to continue with the therapeutic break or to reinitiate treatment with the same drug, or a different one.

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**Bibliography**

**RESPONSE OF THE AUTHORS:**
We have read the various letters to the Editor which have been submitted by readers, some in favour and some against, in the debate around whether therapeutic holidays are appropriate or not. This is a controversial topic, about which we have no scientific evidence. Hence the difference of opinion, although it is clear that above all there is, in all those who have written (as well as in ourselves), an underlying fear of harming the patient in any way. We believe the debate enriches our knowledge, and so we thank those readers who have expressed their opinions, encouraging others to continue this type of discussion on any subject published in the Journal.

**Manuel Sosa Henríquez**  
Mª Jesús Gómez de Tejada Romero  
Jorge Malouf Sierra