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Clinical case discussion: therapeutic holiday, yes or not?

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Presentation

We introduce a new, special type of document, in which, within the Journal itself, we will debate a currently controversial theme which will allow the reader to reflect and, above all, participate by contributing their opinions in the form of letters to the Editor.

On this occasion, we address the matter of treatment holidays, using a clinical case. Two reasoned opinions, in favour and against, are expounded below, with the sole aim of setting out the arguments and stimulating the contribution of readers to the debate.

Clinical case

A female patient currently 63 years of age, who attended a clinic for the first time in July 2004 at the age of 53. She was referred by her family doctor due to a clinical picture of back pain, which had developed over a period of several months. At this first visit a lateral dorsal-lumbar spine X-ray was requested (Figure 1) which showed the existence of a lumbar vertebral fracture.

In terms of personal history, the patient had an early menopause at 35 years of age, without there being any disease to which would have caused it, for which hormone replacement therapy for 5 years was indicated. Similarly, hypercholesterolemia was diagnosed, for which the patient followed a diet and took simvastatin irregularly. The patient does not consume tobacco or alcohol, is sedentary and has no other history of interest. She does not take any other medication, apart from the aforementioned statin.

The results of the tests carried at the first visit were completely normal. The data relating to bone mineral metabolism are shown in Table 1. The levels of vitamin D, measured as 25-hydroxycolecalciferol (25-HCC), were 22 ng/mL. The evaluation of risk at 10 years using both the FRAX® scale and Qfracture® is shown in Table 2.

The densitometry values are shown in Table 3 and their development over time in Figures 2 and 3.

Treatment indicated for the patient was in the form of general measures such as walking daily for an hour, increasing intake of skimmed milk products, calcium and vitamin D supplements, and alendronate with vitamin D weekly. The patient was evaluated by the rehabilitation service which provided physiotherapy for a period of 2 months, reducing her back pain. The patient has continued with the treatment indicated for 10 years, which she tolerates well, without secondary effects, that she occasionally forgets the calcium and vitamin D supplements. She has had no falls or fractures during this period of treatment.

At the last visit, which occurred in February 2014, after 10 years of treatment, she brought along a report from her family doctor which asked our opinion regarding the possibility of discontinuing the patient's treatment and giving her treatment holidays.

Reasoned arguments

A) Reasons for maintaining this patient's treatment (NO to treatment holidays)

Manuel Sosa Henríquez and Mª Jesús Gómez de Tejada Romero

Our main aim in instigating treatment for osteoporosis is to avoid the appearance of fragility fractures[1], which is the clinical complication of this disease, whether it the first fracture before it has even been presented or, if it were already there, successive ones.

Equally important are the consequences of the fractures, that is to say the appearance of pain and the worsening of the quality of life. So, with the treatment, we are also attempting to avoid or reduce this pain or improve the patient's quality of life[2].

The purely clinical reasons (which is to put economic reasons and the patient's personal reasons to one side) for discontinuing a particular treatment, for osteoporosis or for any other disease, in our view are:

1. Due to the disease being cured. Hence, we stop an antibiotic when the infection ceases, or an anti-inflammatory once the inflammatory process is cured. This is not the case with osteoporosis, which is a chronic disease, with profound microstructural changes which are not cured.

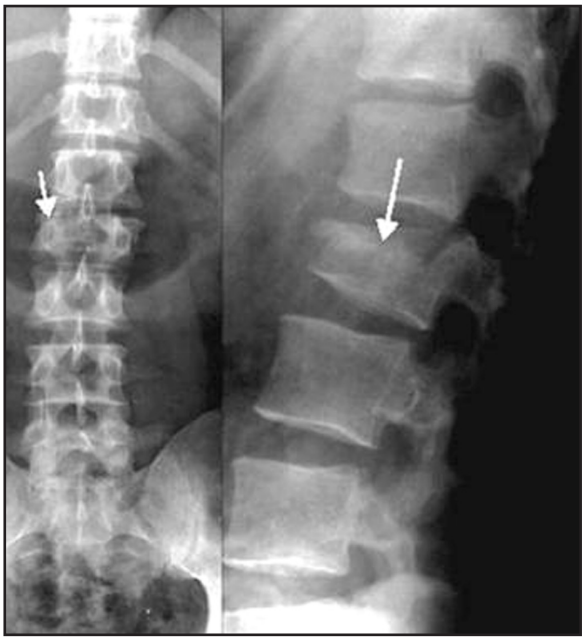
2. Due to the loss of effectiveness of the drug used. Using the same example as before, some micro-organisms may develop resistance to an antibiotic, which, having initially been useful, stops being so. In the field of osteoporosis this is much more complicated to define, given that, on the one hand, fractures have a multifactorial etiopathology and on the other, the drugs we have available reduce the risk of fracture but do not eliminate them completely. To simplify the response, we are assuming "treatment failure" criteria as indicated by Díez Pérez et al[3].

3. In some cases, a limit is established before the use of a drug. Hence, teriparatide may be used over a maximum period of 2 years, according to the indication given in its data sheet. Or zoledronate, in which, according to recently published data, after 5 years of use the reduction in the risk of fracture is the same whether it continues to be administered or is discontinued[4].

4. Another reason for discontinuing a drug is the appearance of secondary effects which overcome the beneficial effects of its use against the disease for which it is prescribed. For example, in the treatment of osteoporosis with SERMs the appearance of thromboembolic phenomena necessitates its cessation and substitution by another type of antiosteoporotic drug.

Taking these reasons into account, in the case which occupies us is there any reason for stopping treatment in this patient? The treatment has been maintained over 10 years, and even with her being a high risk patient, with a previous vertebral fracture, in all this time she has not suffered any new fractures. Therefore the treatment up to this point in time has been successful, having achieved exactly what was expected of it. In addition, the patient is asymptomatic, her biochemical markers for bone remodelling are normal and her bone mineral density has not stopped increasing since the therapy was initiated.

Figure 1. Lateral and anteroposterior X-rays of the patient's spine. The arrows indicate the vertebral fracture (L2)



In recent years however, and on the basis of descriptions in the literature of cases of osteonecrosis of the jaw (ONJ) and atypical femoral fractures in patients being treated with bisphosphonates[5,6], a strand of opinion is gaining strength towards ceasing treatment solely because of the fact that "it has carried on for some considerable time", "because there are no data on its safety after a certain number of years" or "due the risk of the appearance of the same type complication as osteonecrosis of the jaw or atypical femoral fracture". It seems to us that these justifications don't carry much real weight. In terms of duration of treatment, perhaps we can raise this question in the treatment of other chronic diseases such as AHT or diabetes. A pathology, while it exists, should be treated, *a priori*, and in the absence of complications or secondary effects, the treatment should be maintained with the drug of choice if it is being effective.

On the other hand, the bisphosphonates are quite safe drugs whose single demonstrable adverse effect is a lesion in the oesophageal mucosa, which is avoided through postural measures after its oral administration. It is true that there are no reliable safety data for such a long period of treatment with bisphosphonates. However, it is difficult for these to be collected (at least not within the terms of a clinical trial, with a high number of patients, randomised, controlled and double blind to ensure reliability) because clinical trials in the

Table 1. Biochemical data related to bone mineral metabolism. 25-HCC: 25-hydroxycalciferol. TRAP: tartrate resistant acid phosphatase. P1NP: amino-terminal propeptide of procollagen type 1. CTX: carboxy-terminal telopeptide of collagen type 1. NA: not applicable

Parameter	Reference range	2004	2014	Percentage change compared to baseline
25-HCC (ng/mL)	30.0 - 80.0	22	51.8	57.5%
PTH (pg/mL)	15 - 88	54.2	29.9	-81.2%
Calcium (mg/dL)	8.5 - 10.5	8.9	9.3	4.3%
Phosphorus (mg/dL)	2.5 - 4.9	3.2	3.2	0%
Osteocalcin (ng/mL)	11 - 43	8.6	13.45	55.8%
TRAP (UI/L)	0.0 - 3.3	2.4	2.9	17.2%
P1NP (ng/mL)	Premenopausal: <30.1 Postmenopausal: <37.1 Men: <36.4	NA	22.54	NA
CTX (ng/mL)	0 - 0.5	0.4	0.15	-166.6%
Corrected calcium (mg/dL)	8.5 - 10.5	9	9.4	3.1%

Table 2. Estimation of the risk of fracture at 10 years at the first visit

Estimated absolute risk	FRAX®	QFRACTURE®
Any fracture *(Major)*	15	6
Hip fracture *(hip)*	2.7	2

field of osteoporosis only last 3 to 5 years. Once approval for the drug's use is given the study concludes. There are very few long term follow up studies, and in these the loss of numbers of patients is so high that it begins to raise questions about whether the remaining population is representative of that at the start of the study. Therefore, once a drug comes onto the market it is the clinical experience which matters. Then, if there are no adverse effects, and the drug continues to be effective, the clinical experience has nothing to say against the continuation of the treatment.

The feared secondary effects associated with the long term treatment with bisphosphonates, attributed to its powerful antiresorptive effect, such as osteonecrosis of the jaw or atypical fractures, are not a real problem. Osteonecrosis of the jaw associated with bisphosphonates is a complication which mainly appears in cancer patients treated with these drugs for their bone metastases, who, in addition, have received other powerful treatments (cytostatics), and in whom the bisphosphonates are used at doses much higher than those used in the treatment of osteoporosis[5]. On the other hand, while the precise etiopathology of ONJ is not known, these days it has already been identified as having a multifactorial etiopathology, which would include factors not only related to the treatment received by the patient (the bisphosphonates certainly, but also the glucocorticoids), but also the presence of concomitant diseases (such as diabetes mellitus or rheumatoid arthritis), as well as the concurrence of dental intervention (extraction, implants, etc.), accompanied by an infectious component[7]. Yet, even if this were not enough for ONJ not to be considered as a real problem in the treatment of OP with bisphosphonates, it is known that up to 25% of the cases of ONJ reported, bisphosphonates were not taken[5,8]. In those cases described in osteoporotic patients treated with bisphosphonates, studies of its incidence talk in figures of around 1/100,000 patients/year and even less than 1/100,000 patients/year[9]. In the reference study of zoledronate (HORIZON), which considered ONJ as an adverse effect, the appearance of only two cases were confirmed, one of which occurred in the placebo group[10]. A systematic review, which evaluated whether patients in treatment with bisphosphonates, both I.V. and orally, had a greater risk of suffering ONJ before the performance of a dental implant than those not being treated with this

Table 3. Densitometry values over 10 years of development. BMD: bone mineral density

Year	BMD L2-L4	T-score L2-L4	BMD femoral neck	T-score femoral neck	BMD total hip	T-score total hip
2004	0.655	-3.7	0.607	-2.1	0.778	-1.3
2005	0.717	-3.1	0.639	-1.8	0.845	-0.8
2006	0.734	-2.9	0.648	-1.8	0.850	-0.8
2007	0.765	-2.6	0.638	-1.8	0.843	-0.8
2008	0.744	-2.8	0.671	-1.5	0.852	-0.7
2010	0.744	-2.8	0.638	-1.8	0.825	-1.0
2011	0.757	-2.7	0.647	-1.8	0.844	-0.8
2012	0.777	-2.5	0.646	-1.8	0.870	-0.6
2014	0.776	-2.5	0.673	-1.5	0.884	-0.5

drug, concluded that treatment with bisphosphonates was not a contraindication for carrying out this intervention[11]. Increasing numbers of researchers are concluding that ONJ is such an infrequent complication in patients treated with bisphosphonates for osteoporosis that its risk does not justify cessation of long term treatment, and more so when this is a treatment which effectively reduces the risk of fracture, a complication whose incidence is incomparably higher than that of ONJ, as well as its morbidity, mortality and socioeconomic cost.

On the other hand, atypical femoral fractures are currently the principal argument in favour of the suppression of treatment with bisphosphonates, since in various epidemiological studies it has been established that there is a definite association between the risk of developing an atypical fracture and the period of time over which bisphosphonates are used[12]. However, it is also certain that cases of this type of fracture have been described in patients who are not taking bisphosphonates, but with other antiresorptive drugs such as denosumab[13], and even others not used for osteoporosis, such as proton pump inhibitors and the glucocorticoids. It has also been associated with other pathological conditions, such as hypophosphatasia, vitamin D deficit and rheumatoid arthritis[14]. Overall, the risk of atypical femoral fracture is very low. A study carried out by Black et al. which analysed femoral fractures which occurred during three clinical trials (FIT, FLEX, and HORIZON, carried out with alendronate and zoledronate), found that in a total of 14,194 women included in the study there were 283 femoral fractures, of which only 12 were atypical[15]. Its incidence has been estimated at 32 cases/million patients/year[12] or 1.78/100,000 patients/year[16], and even though the same studies found an increase in incidence with years of treatment –of 10%/year[15] and 113.1/1000,000 patients/year[16]– even this incidence is not sufficient to affect the risk/benefit ratio of these drugs. With the evidence currently available it is not possible to establish a causal relationship between prolonged treatment with bisphosphonates and the appearance of atypical fractures, it being probable that these drugs play a role in their development, but not possible that they provide the sole condition for the development of these fractures[17].

The final reason which might justify the discontinuation of treatment is the observation that the biphosphonates have a certain residual effect and that once stopped the reduction in the risk of fractures is prolonged without the continuation of the drug. The reference study for alendronate, called the FIT study, confirmed that after a follow up of an average of 4.3 years, patients who took alendronate had a reduction in the risk of morphometric vertebral fractures of 47%, clinical fractures of 55% and hip fractures 51%[18].

The researchers in this study extended it a further 5 years, calling it the FLEX study, comparing the reduction in risk of fracture between those who continued to take alendronate and those who stopped taking it. It was observed that when the treatment was stopped there was a residual effect on the reduction in risk of non-vertebral fracture, but in contrast, the risk of vertebral fracture increased in comparison with those patients who had continued taking the drug, in whom the reduction in the risk of vertebral fractures was 55%[19].

But not even taking the drug correctly gave the patients 100% protection. Or, stated in another way, the risk never reduced to 0%. However, there is an additional risk factor which is highly significant, and inescapable, namely age. In our patient, only taking the age factor into account, her risk of

fracture has increased because she is 10 years older. If we now suggest the patient has "treatment holidays" (a euphemism for cessation of treatment) we are ignoring the increased risk due solely to the fact that she is 10 years older. What, then, is the aim of initiating treatment for osteoporosis? To avoid the occurrence of fractures, if possible throughout the patient's life? Or to delay their appearance until 10 years later?

In this patient the treatment for osteoporosis has been effective to date. There have been no secondary effects or complications of any kind. The biochemical markers for bone remodelling are normal, there is no "oversuppression" of bone remodelling. The BMD is increasing. And the patient is 10 years older. Solely for this reason her risk of new fractures is now even greater. If we stop the patient's treatment (that is, give her treatment holidays) simply because she has been taking it for 10 years, it is possible that the protection achieved would be reduced to the point at which it no longer counteracts the increased risk of fracture which is due to the same fact, the patient being 10 years older.

In our opinion, therefore, stopping treatment for this patient is neither necessary nor advisable.

B) Reasons for carrying out treatment holidays in this patient (YES to treatment holidays)

Jorge Malouf Sierra

As has been stated earlier, the aim of any treatment for osteoporosis is to reduce the risk of fragility fractures. These types of fracture appear when the resistance of bone is not capable of maintaining the integrity of bone tissue and the most innocuous biomechanical forces provoke a collapse in bone structure.

The NICE guides for the assessment and treatment of fragility fractures 20 suggest that an assessment of the risk of fracture should be made in women below 65 years of age, only if they have other associated risk factors, among which may be:

- Previous fragility fracture.
- Current use of glucocorticoids.
- History of fractures.
- Family history of femoral fractures.
- Secondary causes of osteoporosis.
- Low body mass index (lower than 18.5 kg/m^2).
- Tobacco use.
- Consumption of more than 14 units of alcohol per week.

In the case of our patient, it may be considered appropriate to assess the risk of fracture by means of DXA, given that she has a vertebral fracture. However, she has only one such fracture. Ismael et al. reported in 2001 that vertebral fractures are a predictive factor for subsequent vertebral fractures, as well as hip and non-vertebral fractures. However, the increase in risk was significant only after two or more vertebral fractures[21].

Also, the patient's clinical history does not confirm whether this fracture was related to any trauma, or what degree of fracture it was. It is reported that the number and severity of fracture(s) increases the risk of fractures[22], independently of the patient's BMD. Even so, the BMD which best predicts the risk of fracture is that in the femoral neck.

Figure 2. Change in bone mineral density in the spine

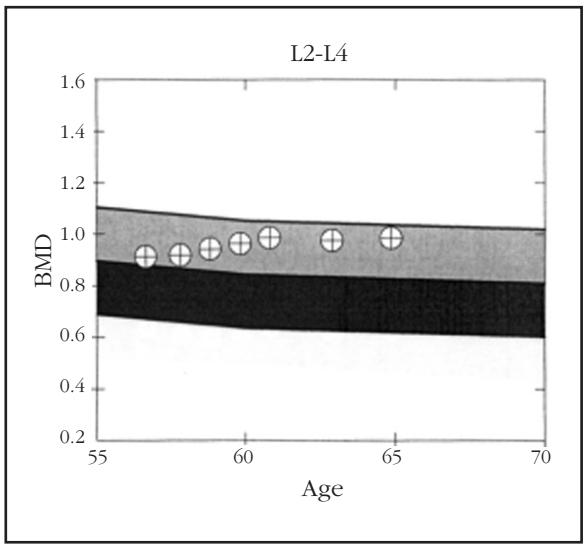
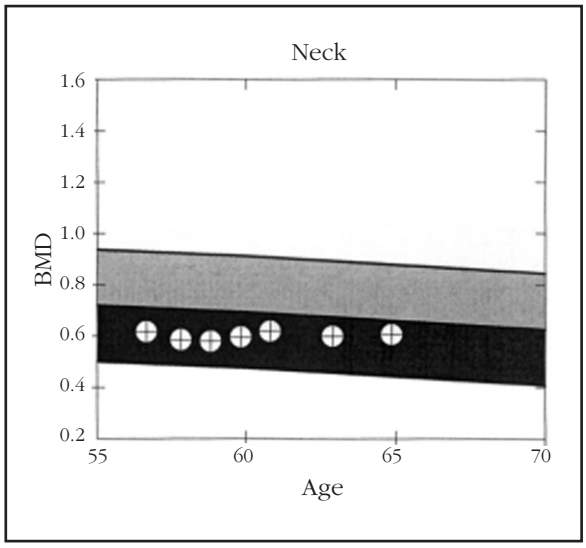


Figure 3. Change in bone mineral density in the femoral neck



Returning to the clinical case: during 10 years of follow up and periodic densitometries the patient never had a BMD in the femoral neck compatible with osteoporosis, this being a T-score lower than -2.1 at the start of the development of this pathology.

As is also mentioned earlier, one of the most significant risk factors for fractures is age. At the start of treatment, when the patient was 53 years of age, the risk of fracture was very low, and although the BMD in the lumbar spine was low, there was not a very high risk of fracture – vertebral or hip.

The bisphosphonates are antiresorptives which have a great affinity with bone tissue. Patients who receive a bisphosphonate over long periods will have bisphosphonate bonded with the bone for a long time. This has meant that, in recent years, various adverse effects have appeared, which are usually observed after a period of treatment. These adverse effects are atypical hip fracture and bisphosphonate-related osteonecrosis of the jaw (ONJ). The latter was reported for the first time by Marx in 2003[23], but to date, although it is known that there is a relationship between the prolonged use of bisphosphonates and this pathology, the strength of this relationship is not clear. It is known that there are various risk factors which increase the probability of suffering ONJ, such as the duration of treatment, genetic factors and demographic factors, such as age, among others[24].

The patient in the clinical case is a woman of over 60 years of age who has been receiving oral bisphosphonates for 10 years, which increases the risk of the appearance of ONJ. On the other hand, the patient's long period of treatment with bisphosphonates also provides some advantages, such as the fact that the bisphosphonates continue to be released by the bone over a long period of time, reducing the risk of fracture in spite of the patient not continuing with the treatment. This strategy is known as a treatment holiday[25].

The longest placebo controlled study there has been was with risedronate, and the results regarding its efficacy and safety come after 5 years of treatment. This trial assessed the reduction in risk of fracture and demonstrated an additional effect during the final years of treatment. During the following year or two the markers for bone remodelling changed little. Although there is no clinical trial which demonstrates that the risk of fracture stays low during this "treatment holiday" period, it may be assumed that, if the markers for bone remodelling don't change, the patient with a low risk of fracture may be protected during this time and it would not be necessary for them to continue to take bisphosphonates 26. Similarly, Black et al. showed that continuing treatment with zoledronic acid for 6 to 9 years did not bring any benefits in respect of a reduction in the risk of fracture[4].

Finally, the Spanish Society for Bone and Mineral Metabolism Research (SEIOMM) has published a document in which it recommends that after 5 years of treatment with oral bisphosphonates all patients be evaluated with aim of assessing the risk of fracture of the particular patient, and thus to decide whether to continue with the bisphosphonate (in cases where the risk is high) or discontinue treatment. In addition, it recommends that in those patients with a T-score above -2.5 in the femoral neck temporary cessation of treatment (treatment holidays) be considered[27].

So, in the case of this patient, the only risk factors which remain are age and history of vertebral fracture. During 10 years of treatment the BMD of the patient has developed satisfactorily, currently being borderline in the spine (T-score: -2.5) and at osteopenic levels (T-score: -1.5) in the femoral neck. These data suggest that the patient should not continue with the treatment with oral bisphosphonates and should have treatment holidays. Later, the patient's risk of fracture should be assessed annually, investigating specifically her BMD, changes in levels of markers for bone remodelling and paying most attention to the progress of her pre-existing vertebral fracture or the production of new vertebral fractures, in which case she should be reassessed for the initiation of treatment, be it with antiresorptive or osteoforming drugs.

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