MANAGEMENT OF ENDOCRINE DISEASE

Treatment breaks in long-term management of osteoporosis

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Abstract

Osteoporosis is a common chronic disease and therefore a long-term management plan based on disease severity, comorbidities, other pharmacological treatments, gender, age and patient preferences is necessary. Consideration of treatment breaks may be included in the long-term management plan if the patient has been treated with a bisphosphonate, the disease is less severe, the response to treatment has been satisfactory and the risk of future fracture is estimated to be low. This perspective reviews the current evidence for long-term treatment with bisphosphonates and off treatment effects. Approaches to decision making and monitoring of treatment breaks are discussed.

Introduction

Fragility fractures are common, affecting 1 in 3 postmenopausal women and 1 in 5 elderly men. Osteoporosis is characterized by low bone mass, deteriorated microarchitecture of the bone and fragility fractures. The diagnosis is based on bone mineral density (BMD) as assessed by DXA; the diagnostic criteria being BMD less than 2.5 standard deviations below peak bone mass corresponding to T-score of the spine or hip < −2.5 (1). The severity of osteoporosis varies greatly between patients. Some are mildly affected with a moderately reduced BMD, T-scores between −2.5 and −3 and no fractures, whereas at the other end of the spectrum, we see patients who are severely affected with multiple fragility fractures including hip and spine fractures that are associated with increased morbidity and mortality (2, 3). This wide spectrum of disease severity calls for an individualized approach to the management of osteoporosis; however, this has not been widely implemented because the reimbursement of osteoporosis treatment in most countries dictates that all patients should initially be treated with oral bisphosphonates. Therefore, the individualized management approach is mainly applied to the considerations about treatment duration and change of treatment. This perspective will
focus on the treatment duration and treatment break aspects of the long-term treatment of osteoporosis with bisphosphonates.

Osteoporosis is a chronic condition and therefore the concept of treatment breaks is counterintuitive. The one thing that makes this concept worth considering anyway is the fact that bisphosphonates adhere very strongly to bone surfaces and therefore bisphosphonates remain in the bone for years after stopping taking the drug and the antiresorptive effect of bisphosphonates is maintained (4). It can therefore be argued that a treatment break with bisphosphonates is not a treatment break, merely a discontinuation of administration of the drug, during which the antiresorptive effect of bisphosphonates will weaken over time.

The other antiresorptive treatments available; denosumab, hormone replacement therapy, selective estrogen receptor modulators and the bone-forming treatments; teriparatide and abaloparatide have no sustained effect after stopping administration of the drugs. After discontinuation of denosumab a rebound activation of bone turnover to a level well above pretreatment level is seen. This is accompanied by rapid bone loss and possibly an increased risk of vertebral fractures (5). It is unclear if the rapid bone loss following discontinuation of denosumab can be prevented fully by initiation of bisphosphonate treatment (6). This is currently being investigated in a number of clinical studies. For the other antiresorptive and bone-forming treatments, a gradual return to the pretreatment BMD is observed after stopping treatment. Therefore, discontinuation of anti-osteoporosis treatments other than bisphosphonates should be considered carefully and if protection against fractures is still wanted another treatment should be initiated.

**Long-term effect of bisphosphonate treatment and effects of stopping treatment**

Our understanding of the long-term effects of bisphosphonates is predominantly based on the findings of the extensions of the pivotal fracture prevention studies of alendronate and zoledronic acid. The fracture prevention study of alendronate, the FIT study (7) was extended into the FLEX trial (8). The fracture prevention study of zoledronic acid, the HORIZON study (9) was extended into the HORIZON Extension trial (10). Both extension studies included relatively few patients compared to the original studies and the statistical power to detect differences in fractures, especially non-vertebral fractures was therefore limited. There is no evidence of treatment effects of bisphosphonates or any other anti-osteoporosis treatment beyond 10 years from clinical trials.

The FLEX study demonstrated that continuing alendronate for 10 years led to a continuing increase in lumbar spine BMD and a stabilization of BMD at the hip compared to stable BMD at the lumbar spine and BMD at the hip decreasing toward baseline BMD in the women who discontinued alendronate after 5 years. The incidence of non-vertebral fractures was similar between the two groups; however, the incidence of clinical vertebral fractures was higher in the women stopping alendronate compared to the women continuing alendronate (8).

Similarly, the HORIZON Extension study showed that BMD of the spine continued to increase and BMD of the hip remained stable in women continuing treatment with zoledronic acid for 6 years. In women stopping treatment after 3 years, BMD at the spine was stable, whereas hip BMD decreased toward baseline. The incidence of non-vertebral fractures was similar during years 3 to 6 in women continuing and discontinuing treatment with zoledronic acid, but the incidence of morphometric vertebral fractures was higher among the women stopping treatment (10).

The BMD changes in the continuously treated women are in accordance with the current understanding of the mechanism of action of bisphosphonates (4). Bisphosphonates inhibits the resorptive capacity of osteoclasts and therefore the remodeling space in trabecular as well as cortical bone is reduced and these changes lead to the initial increase in bone mass seen with bisphosphonate treatment. The bone tissue becomes more mineralized with time and therefore bone with reduced remodeling activity is more mineralized, which leads to a slower and more modest increase in bone mass. Once the remodeling space is filled up the majority of the increase in BMD seen with bisphosphonates will have occurred and only minor increases due to increased mineralization can be expected. This is reflected in the initial increases in BMD at the spine and hip seen in clinical studies with bisphosphonates. After a few years, the BMD remains stable at the hip sites, but seems to continue to increase at the spine. It has been speculated that the latter is caused by other factors such as degenerative changes, osteoarthritis and calcification of aorta (11). As these age-related changed do not affect the BMD measurements
at the hip, the hip is the most reliable site for observing long-term changes.

When stopping bisphosphonate treatment BMD is generally stable at the lumbar spine, but decreases at the hip site, suggesting a lessening of the antiresorptive effect of the bisphosphonates and a reactivation of remodeling activity. The fracture outcome of the FLEX and the HORIZON extension studies suggests that the lesser suppression of bone resorption may be sufficient to prevent non-vertebral fractures in women who have had bone remodeling substantially reduced for 3–5 years (8, 10). This can perhaps be understood in the context of the imminent fracture risk seen in patients with a recent fragility fracture (12, 13). The imminent fracture risk after a fragility fracture is present in 1–3 years after a fracture and thereafter the fracture risk decreases to a more modest level, which is still higher that the fracture risk seen in the background population (13). Although not all women included in the FIT and the HORIZON studies had recent fragility fractures, it is well known that fractures often are the reason why women and men get investigated for osteoporosis and subsequently enrolled in clinical trials. It can therefore be speculated that one reason why the risk of non-vertebral fractures is maintained at a low level after stopping treatment is that the patients have passed the years of high imminent fracture risk while on treatment and as the risk is reducing just because time is passing since the last fracture less suppression of bone turnover is sufficient.

The FLEX and the HORIZON extension studies also showed that stopping treatment was associated with an increased risk of vertebral fractures (8, 10). The remodeling activity in untreated postmenopausal women is higher in trabecular bone (14, 15), which constitutes the vast majority of the vertebral bodies (16) and therefore the weakening of the suppression of bone resorption that follows stopping the treatment will probably lead to reoccurrence of some remodeling activity on trabecular surfaces more rapidly than in cortical bone. Increased remodeling activity and the associated destabilization of the trabecular structure is probably more important causes of vertebral fractures than low bone mass in it-self, whereas non-vertebral fractures are more dependent on bone mass in addition to falls (17). This concept fits with the very rapid reduction in the risk of vertebral fractures seen with strong antiresorptive treatments, the reduction occurring before substantial increases in lumbar spine bone mass are seen. The reduction in non-vertebral fractures takes longer time and is more dependent on increases in bone mass at the hip site.

The evidence of the fracture outcome in patients on treatment breaks outside of clinical trials is still sparse and inconclusive (18, 19).

Post hoc analyses from the FLEX study aiming at identifying subgroups of women who were at increased risk of clinical fractures during the treatment break have demonstrated that women with low hip BMD and higher age had an increased risk of fractures (20). In the HORIZON Extension study, prevalent vertebral fractures and low hip BMD were demonstrated to predict vertebral fractures during the treatment break. Low hip BMD, prevalent vertebral fractures and non-vertebral fractures during the active treatment period predicted non-vertebral fractures during the treatment break (21). Bone turnover markers at the entry into to FLEX or the HORIZON Extension studies did not predict increased risk of fracture.

It has also been investigated if changes in BMD or bone turnover markers 1 year after stopping alendronate predict fractures in the FLEX study, but this was not the case (20). These findings have made it difficult to make recommendations regarding in which patients to consider treatment breaks and in which patients not to and not the least how to monitor patients during a treatment break.

Why consider treatment breaks?

Some patients are at increased risk of fractures when stopping bisphosphonate treatment and it seems difficult to identify a subgroup of patients in whom it may be safe to consider a treatment break. Furthermore, we have no evidence-based knowledge about how best to monitor patients during treatment breaks. Why then consider treatment breaks at all?

The first argument for considering treatment breaks came from physicians experiencing patients being reluctant to continue treatment of a condition with no symptoms and pharmaco-surveillance analyses demonstrating that compliance with oral bisphosphonates outside clinical trials was poor (22). This gave rise to the argument that since so many patients by themselves decide to take treatment breaks, a better understanding of the consequences of treatment breaks and an optimized treatment strategy are needed in order to discuss long-term management of osteoporosis with the patients. Next came the reports of rare adverse effects associated with long-term antiresorptive therapy, including osteonecrosis of the jaw (23), atrial fibrillation (24) and atypical femur fractures (25, 26). Osteonecrosis of the jaw is very rarely seen in patients treated with
biphosphonates for osteoporosis and is in the vast majority of cases mild and self-limiting. The suggested increased risk of atrial fibrillation has not consistently been confirmed. Osteonecrosis of the jaw and atrial fibrillation are therefore no longer driving the argument for treatment breaks; the argument is the risk of atypical femur fractures. The risk of atypical femur fractures in patients treated with bisphosphonates is very low. It is difficult to make a precise estimation of the incidence due to its rarity and the weakness of health care registers in capturing the diagnosis correctly. Schilcher et al. made a huge effort in estimating the incidence rate by reviewing radiographs of all patients with a subtrochanteric femur fracture in their database (27). They found that the incidence was 0.02/1000 patients treated for 1 year and increased to 1.1 per 1000 patients treated for 4–5 years. They also saw that the incidence was reduced to nearly pretreatment level within a year after stopping treatment: 0.3/1000. It is good news that the risk decreases quickly upon stopping treatment, but on the other hand, difficult to understand from a bone biology perspective. If this rare event is caused by reduced remodeling or increased mineralization or a combination of the two, it is difficult to understand how the risk of AFF can return to pretreatment level within a year when studies have shown that normal remodeling activity will not have resumed within a year. So, if this is true, the risk reduction either does not need full restoration of the pretreatment bone physiology, a weakening of the suppression of bone turnover is sufficient or it suggests that other factors play a role; bisphosphonates have been suggested to have antiangiogenic effects.

Abrahamsen et al. used the Danish registers and found that more than 60 000 individuals had received treatment with oral bisphosphonates and that more than 2400 had received the treatment for more than 10 years with high persistence (28). They found that treatment with oral bisphosphonates for 5–10 years continued to reduce the risk of hip fractures. Since this was a register-based study they could not look specifically for AFFs, but the risk of subtrochanteric fractures, which in most cases are typical osteoporotic fractures but also includes the AFFs did not increase with time and even if all subtrochanteric fractures were considered AFFs then stopping alendronate after 5 years compared with continuing for 10 years would prevent 26 hip fractures and cause less than one subtrochanteric fracture in 1000 patients.

A treatment break should be carefully considered in the individual patient

The most important argument in favor of considering a treatment break in a patient who have been treated with alendronate for 5 years or longer or zoledronic acid for 3 years or longer are that continued administration of the treatment may not be needed to protect against future fractures as the slowly diminishing effect of the bisphosphonates in the bone may be sufficient. In addition, stopping the administration of the treatment may reduce the risk of AFFs. The most important argument against considering a treatment break is the subsequent risk of vertebral fractures. Due to many pharmaco-economic evaluations of the treatments for osteoporosis where hip fractures are the factor driving the estimates, we tend to forget the importance of vertebral fractures. Studies have shown that clinical vertebral fractures affect patient’s lives to a similar extent as hip fractures; days of limited activity after a vertebral fracture or a hip fracture are similar (29). The reason why vertebral fractures do not seem to be equally important in the pharmaco-economic calculations is that even clinical vertebral fractures are insufficiently captured in the health care registers because these patients are often not hospitalized, but treated in the primary health care setting. The costs related to these clinical fractures are therefore not captured. Morphometric non-clinical fractures are also associated with morbidity and increased risk of future fractures and therefore prevention of any vertebral fracture, clinical or non-clinical contributes to the pharmaco-economic benefit of treatment.

The individualized approach to treatment break should aim at identifying patients in whom a treatment break is associated with limited risk of suffering fractures during this treatment break. Many guidelines have been published over the last decade. Most of them agree that patients at moderate-to-high risk of fracture should continue treatment, whereas patients considered at low to moderate risk may consider treatment break. Moderate-to-high risk of future fracture is in most guidelines defined as a low BMD at the hip (T-score < −2.5), a major fragility fracture within the last 3–5 years, prevalent vertebral fractures or a previous hip fracture. Some guidelines also include an evaluation of future fracture risk based on FRAX or a similar tool although FRAX and the other fracture risk predictive tools have not been validated in patients on treatment. An example of such a guideline is the ASBMR guideline (Fig. 1) (30).

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How to monitor patients on treatment break?

There is no evidence to guide the monitoring of patients during treatment breaks. Based on the FLEX and the HORIZON extension studies, the changes in BMD or bone turnover markers do not predict subsequent fractures (20, 21). Furthermore, these studies only provided information about the first treatment break. However, these patients had osteoporosis and indication for treatment of the disease some years ago and since both the FLEX and HORIZON extension studies showed that hip BMD declined toward pretreatment levels during the treatment break, the disease and the indication for treatment will potentially reappear. Therefore, it does not seem appropriate not to monitor these patients for reappearance of the disease and different suggestions for monitoring and response to the outcome of the monitoring have been made.

Based on the FLEX study where the incidence curves for vertebral fractures separate after approximately 2 years (8), experts have suggested a fixed term of 2 years for a treatment break and then resume treatment after 2 years without monitoring during this period.

An incident fracture, at least if it is in the category of a major osteoporotic fracture would be considered an indication of reappearance of the disease and for restarting treatment by most clinicians.

It has also been suggested to restart treatment if a significant BMD loss occurs as this would indicate that there is no longer suppression of bone remodeling. The rationale behind this being that the disease will reappear when bone turnover is no longer suppressed. The difficulties with this assumption are that it is clear from the FLEX and the HORIZON extension studies that patients on average will experience a significant bone loss at the hip with time off treatment and that this bone loss was not associated with non-vertebral fractures in the studies. With the more widespread use of biochemical markers of bone turnover in the clinic, another option would be to monitor the suppression of bone turnover and resume treatment when bone turnover is no longer suppressed.

When interpreting the changes in BMD or bone turnover markers the variability of these measurements should be taken into consideration. In most clinics, the least significant changes for spine and hip BMD are 3 and 5% respectively. The variability of the bone turnover markers is larger and the blood samples should optimally be collected at the same time of day and for the resorption marker CTX also in the fasting state. The least significant changes may vary between laboratories but are between 15 and 25% (31).

In many ways, these considerations are similar to the considerations of treatment failure in patients on treatment. Diez-Perez et al. suggested that treatment failure can be considered in compliant patients with no competing causes for fracture or bone loss, such as for example vitamin D deficiency or thyroid disease, who have been treated for at least 12 months, if two or more fractures occur, if a significant BMD loss is seen or if bone turnover markers are not suppressed.

Once the decision has been made if the patients should be monitored by absence of fracture, BMD and/or bone turnover markers, the next question is how frequently patients on treatment break should be monitored. The clinical experience and studies suggest that there is a large variation in the rate by which the suppression of bone turnover weakens and therefore how quickly bone loss resumes when stopping especially orally administrated bisphosphonates (32). This was not seen in the FLEX study, probably because patients participating in a clinical trial are more compliant that patients outside clinical trials.
It has been suggested to perform DXA after 2–3 years and if BMD is stable continue the treatment break and monitor with DXA after an additional 2–3 years (30). Restarting treatment should be considered if a significant BMD loss occurs.

If bone turnover markers are available, it can be suggested to measure s-CTX and/or s-P1NP when considering a treatment break. If the markers are not suppressed, a treatment break should probably not be considered and the reason for the non-suppressed markers should be investigated. If, however, turnover markers are suppressed then stop the treatment and monitor markers after 6 months and thereafter at regular intervals and consider resuming treatment when turnover is no longer suppressed.

In order to answer the many questions related to identification of patients who can have treatment breaks and those who cannot, how best to monitor patients during treatment breaks and when to restart treatment, more research is clearly needed. Another interesting topic that has not been investigated is if the patients should restart the same treatment and be treated for another 3–5 years or if the patients can be protected from future fractures by less frequent administration of the same drug or by shifting to a less strong antiresorptive treatment, like SERM.

This perspective is focused on treatment breaks in patients treated with alendronate or zoledronic acid as these are the treatments investigated in clinical trials large enough to investigate fractures in patients off treatment. Similar studies have not been performed for the other bisphosphonates available, but the recent TRIO study suggests that the off treatment effect on bone turnover markers are similar between the mostly used oral bisphosphonates (33). On the contrary, these considerations do not apply to treatment with denosumab, where a rebound activation of bone turnover and a rapid bone loss are seen when stopping the treatment. Therefore, treatment breaks should not be considered in patients treated with denosumab. Furthermore, it is currently not known what the best sequential treatment strategy after denosumab is (6).

Treatment breaks in patients with osteoporosis treated with bisphosphonates should be considered individually. The arguments in favor of a treatment break are to avoid treatment in patients that will not benefit from the treatment in form of fewer fractures and a reduced risk of adverse events, the arguments against are that treatment breaks are associated with an increased risk of clinical fractures, and it has proven difficult to identify the patients carrying that risk. Treatment breaks should therefore only be considered in patients at low risk of future fractures. The optimal duration and the optimal monitoring of the treatment break are currently unknown.

Declaration of interest
B Langdahl is an associate editor of the European Journal of Endocrinology. B Langdahl has received research funding to her institution from Amgen and Novo Nordisk. B Langdahl serves on advisory boards and speaker’s bureau for Eli Lilly, Amgen, UCB and TEVA.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received 9 July 2018
Revised version received 26 October 2018
Accepted 12 November 2018