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SHORT COMMUNICATION

Rebound-associated vertebral fractures after discontinuation of denosumab—from clinic and biomechanics

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Abstract
Summary Rebound-associated vertebral fractures may follow treatment discontinuation of highly potent reversible bone antiresorptives, resulting from the synergy of rapid bone resorption and accelerated microdamage accumulation in trabecular bone.
Introduction The purposes of this study are to characterize rebound-associated vertebral fractures following the discontinuation of a highly potent reversible antiresorptive therapy based on clinical observation and propose a pathophysiological rationale.
Methods This study is a case report of multiple vertebral fractures early after discontinuation of denosumab therapy in a patient with hormone receptor-positive non-metastatic breast cancer treated with an aromatase inhibitor.
Results Discontinuation of highly potent reversible bone antiresorptives such as denosumab may expose patients to an increased fracture risk due to the joined effects of absent microdamage repair during therapy followed by synchronous excess activation of multiple bone remodelling units at the time of loss-of-effect. We suggest the term rebound-associated vertebral fractures (RVF) for this phenomenon characterized by the presence of multiple new clinical vertebral fractures, associated with either no or low trauma, in a context consistent with the presence of high bone turnover and rapid loss of lumbar spine bone mineral density (BMD) occurring within 3 to 12 months after discontinuation (loss-of-effect) of a reversible antiresorptive therapy in the absence of secondary causes of bone loss or fractures. Unlike atypical femoral fractures that emerge from failure of microdamage repair in cortical bone with long-term antiresorptive treatment, RVF originate from the synergy of rapid bone resorption and accelerated microdamage accumulation in trabecular bone triggered by the discontinuation of highly potent reversible antiresorptives.
Conclusions Studies are urgently needed to i) prove the underlying pathophysiological processes suggested above, ii) establish the predictive criteria exposing patients to an increased risk of RVF, and iii) determine appropriate treatment regimens to be applied in such patients.

Keywords Bone antiresorptives · Bone turnover · Denosumab · Microdamage repair · Rebound-associated vertebral fractures

Introduction

In women with hormone receptor-positive non-metastatic breast cancer (HRPBC), optimal adjuvant hormonal therapy should include an aromatase inhibitor (AI) [1]. The use of AI is associated with accelerated bone loss and increased fracture risk [2–4]. Bone loss is mediated by osteoclasts. The maturation from pre-osteoclasts, activity, and survival of osteoclasts depend on the activation of the receptor activator of NF-kB (RANK) by its ligand (RANKL). Denosumab is a human monoclonal antibody that specifically binds to RANKL and thereby reversibly blocks bone resorption leading to decreased bone turnover, increasing bone mineral density (BMD), and reduced fracture risk [5, 6].

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In the randomized, placebo-controlled pivotal trial in women with postmenopausal osteoporosis (FREEDOM trial), denosumab treatment (60 mg subcutaneously every 6 months) over 36 months reduced the incidence of new vertebral fractures by 68 % [5]. In the extension of a phase II study with a small number of postmenopausal women, discontinuation of denosumab was associated with progressively decreasing BMD and with increasing bone turnover markers above baseline values, without detrimental effects on fractures in the safety analysis [7]. Finally, in a post hoc analysis of patients who discontinued in the FREEDOM trial after having received two to five doses of denosumab or placebo, no excess fracture risk vs. placebo was shown during the off-treatment period for up to 24 months after cessation of denosumab [8].

In patients with HRPBC and low bone mass under adjuvant AI therapy, denosumab treatment during 24 months led to significant BMD increases at all sites, including the lumbar spine, compared to placebo [9]. Furthermore, the recently published ABCSG-18 trial showed that subcutaneous denosumab 60 mg every 6 months (Q6M) significantly increased the time to first clinical fracture in these women, including in the subgroup of women with a BMD T-score of less than −1 already at baseline, virtually without added toxicity [10].

Based on these findings, treatment with denosumab was approved in several countries for increasing bone mass in women at high risk for fracture receiving adjuvant AI therapy for breast cancer. However, the clinical consequences of the bone turnover rebound observed after denosumab discontinuation have not been prospectively studied in an adequately designed fracture endpoint trial. No recommendations with regard to appropriate subsequent treatment aimed at maintaining gained bone mass and preserving bone health are available.

We report the case of a woman with early-stage HRPBC treated with adjuvant AI therapy and concomitant bone protection with denosumab during 3 years who developed massively accelerated bone loss and multiple vertebral fractures within a few months after denosumab withdrawal. The pathophysiological background is hypothesized based on clinical and biomechanical considerations.

Case report

Non-metastatic HRPBC was diagnosed and adjuvant AI therapy with exemestane initiated in a 48-year-old premenopausal woman in December 2010. The baseline densitometry was normal in May 2010 with BMD T-scores of −0.6 SD and −0.8 SD at the lumbar spine (LS) and the femoral neck (FN), respectively. In late 2011, osteopenia was diagnosed with BMD T-scores of −2.0 SD and −1.5 SD at LS and FN, respectively. Biochemical markers of bone turnover were increased. Plain radiographs confirmed the absence of prevalent vertebral fractures. Treatment with subcutaneous denosumab 60 mg Q6M and adequate calcium and vitamin D supplementation was initiated in February 2012. In February 2015, after six doses of denosumab, BMD had substantially increased with T-scores of −0.8 SD and −1.3 SD at LS and FN, respectively. Since the end of AI therapy was scheduled for April 2015 and denosumab is not reimbursed any more after AI cessation in our country, therapy with denosumab was discontinued, i.e., not renewed, in February 2015.

In May 2015, the patient complained about progressively worsening low back pain after slipping without falling. In August 2015, magnetic resonance imaging (MRI) of the lumbar spine revealed multiple vertebral fractures (T10, 12; L1–4) with bone marrow edema indicating incident/fresh fractures (Fig. 1). Follow-up BMD testing performed at that time, 6 months only after non-renewal of denosumab treatment and 4 months after AI therapy cessation, revealed an important BMD decrease at the LS (−12 %) and the total hip (−5 %), of an order of magnitude comparable to that of the BMD increase achieved during the three prior years of denosumab therapy (+14 %/+3 %). Vertebral fracture assessment (VFA) revealed a previously unknown additional T8 vertebral fracture. In total, VFA revealed one moderate wedge (T12), two mild (T8; L4), and four moderate biconcave deformities (T10; L1–3), as assessed by using Genant's semi-quantitative technique. Serum levels of bone specific alkaline phosphatase were increased, consistent with high bone turnover (57 μg/L; NR 5.5–27 μg/L). Resorption markers were not measured. Other secondary causes of increased bone loss or vertebral fractures were excluded, including but not limited to multiple myeloma, occult mastocytosis, and silent sprue. Finally, positron

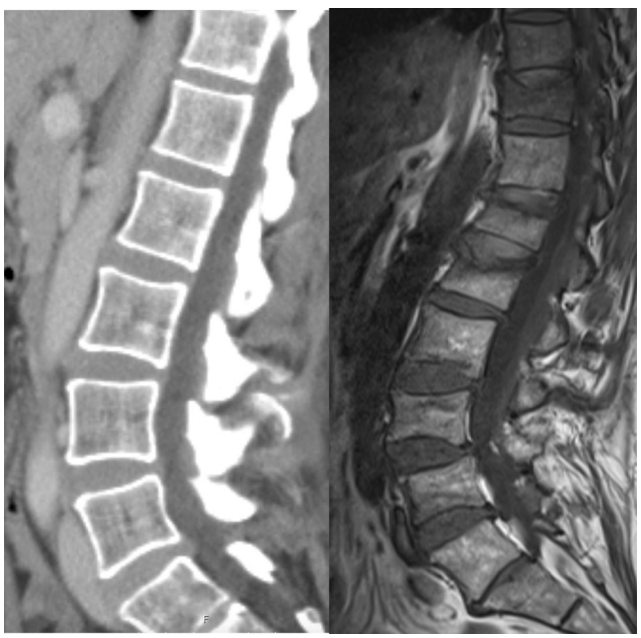

Fig. 1 Sagittal imaging of the lumbar spine from 2011 (*left*; computed tomography) and 2015 (*right*; magnetic resonance imaging—T1 weighted)

emission tomography was negative for any sign of malignancy. The patient gave written informed consent for anonymized case presentation and publication.

Discussion

This is the first case report of incident multiple clinical vertebral fractures after discontinuation of denosumab in a woman with osteopenia and hormone receptor-positive non-metastatic breast cancer treated with an adjuvant aromatase inhibitor.

Osteoporosis-related vertebral fractures result from the accumulation of fatigue microdamage in trabecular bone under physiological cyclic loading [11]. The fatigue properties of human bone were shown in vitro to be related to the accumulation of irreversible strains and the reduction of elastic modulus in both trabecular [12] and cortical bone [13]. In the absence of a repair mechanism, small increases in the applied stress cause a very substantial reduction in fatigue life. Furthermore, peripheral trabecular bone structural units (BSUs) do not only show lower mineralization but also reduced stiffness compared to core BSUs [14]. From their older age, the core BSUs have already experienced a larger number of loading cycles and may therefore be expected to contain more microdamage than the more recent peripheral BSUs, as shown in cortical bone [15].

Vertebral bodies with normal bone mineral density and normal turnover and subjected to normal physiological loads experience low tissue stresses, do not accumulate substantial microdamage, and do not experience fatigue failure. An increase in bone turnover with a negative wall thickness balance, as seen in postmenopausal osteoporosis, produces a cascade of biomechanically deleterious effects: due to the reduced cross-sectional area created by resorption sites, the older tissue at the core of the trabeculae experiences increased tissue stress such that additional fatigue damage accumulates at a higher rate, which may trigger further resorption sites and increase the applied tissue stress even further. In the absence of proper refilling of these resorption sites, the iterative increase in the applied stress on trabecular tissue can dramatically reduce the number of cycles to fatigue failure. As an example, if a single 60-μm wall thickness is resorbed on the quarter of a cylindrical 200-μm trabeculae, the applied axial stress increases by 27 % and fatigue life is reduced by more than an order of magnitude [12]. This self-amplifying mechanism first described by Burr et al. [16] not only explains the progressive occurrence of atraumatic "spontaneous" vertebral fractures in postmenopausal osteoporosis but also introduces an additional independent determinant of fracture to BMD, namely, the extent and distribution of fatigue microdamage, that reduces the number of cycles to failure and therefore the onset of fracture for a given BMD. Seen in this context, patients with high bone turnover such as patients treated with AI are at higher risk of vertebral fractures than predicted by their BMD value alone.

The inhibition of osteoclasts by antiresorptives protects the trabecular architecture from the above deleterious cascade. Bisphosphonates are embedded in the bone matrix, which allows for sustained preservation of bone mass and low accumulation of fatigue damage and avoids an overshoot of synchronously initiated bone remodelling units after withdrawal. In contrast, the bone turnover rebound seen after discontinuation of reversible antiresorptives such as denosumab corresponds to the synchronous activation of gate-waiting osteoclast precursors for enhanced repair of accumulated microdamage. In this situation, the above cascade is reactivated with a fatigue microdamage distribution that is less favorable than at the beginning of the therapy and that may further enhance bone turnover and loss.

In the context of high bone turnover, the number of resorption sites as well as the depth of the resorption lacunae is increased. In patients with thin trabeculae, such as patients with osteopenia or osteoporosis, an increase in resorption depth relative to the thickness of trabeculae may be responsible for trabecular perforation [17]. In addition, in cortical bone, osteoclastic bone resorption proceeds in tunnels with shorter remodelling cycles than in trabecular bone [18]. During of high bone turnover, the increased number and accelerated bone resorption activity of osteoclasts will lead to reduced cortical bone strength. In the human vertebrae, cortical bone is a major contributor to bone strength, especially when the trabecular microarchitecture is deteriorated [19, 20]. Applied to the present case report, these mechanisms could contribute to explain the occurrence of multiple vertebral fractures in a very short period of time after denosumab withdrawal.

We hypothesize that the multiple vertebral fractures in the reported case are the result of the high level of bone remodelling following withdrawal of reversible antiresorptives. The latter leads to bone resorption in a tissue that was continuously loaded, with low accumulation of fatigue damage but without repair during therapy. According to the above mechanism, the high rate of bone turnover and loss developed during the rebound would lead to a high rate of damage accumulation and a shortened vertebral fatigue life.

In the light of a recently published series of three cases with incident severe vertebral fractures in postmenopausal women with osteoporosis early after denosumab discontinuation, our case report adds to the available evidence [21]. It indicates that the observed syndrome may be inherent to the loss of treatment effect after discontinuation of reversible antiresorptives rather than to the underlying cause of osteoporosis, with a frequency of occurrence and a degree of severity related to individual patient factors and to the antiresorptive potency of the drug. We suggest the term rebound-associated vertebral fractures (RVF) for this phenomenon, since the extent and the rapid occurrence of multiple vertebral fractures clearly

differ from typical osteoporotic vertebral fractures. Such RVF are characterized by the presence of multiple new clinical vertebral fractures, associated with either no or low trauma, in a context of high bone turnover (biochemical markers) and rapid loss of LS-BMD occurring within 3 to 12 months after discontinuation (loss-of-effect) of a reversible antiresorptive therapy. Secondary causes of bone loss or fractures must have been excluded.

From a biomechanical point of view, it has been hypothesized that atypical femoral fractures (AFF) emerge from failure of a tensile microdamage repair process in cortical bone possibly related to long-term treatment with antiresorptive agents [22]. Unlike AFF, RVF originate from the synergy of rapid bone resorption with accelerated microdamage accumulation in trabecular bone and appear to be directly related to an excessive stimulation of osteoclasts.

The present case report raises several questions of practical relevance to physicians treating patients with denosumab.

First, is the present observation limited to patients having been exposed to or currently under AI therapy or can it be generalized to postmenopausal women with osteoporosis stopping denosumab?

Aromatase inhibitors induce almost complete estrogen deprivation with rapid bone loss, an effect which in the case of the present patient was superimposed to the physiologic early postmenopausal bone loss. Thus, the reported case may be considered an amplification of rebound effects observed either in older breast cancer patients or in younger postmenopausal women not treated with an AI. Through cumulative (synergistic?) effects, it may have revealed in a single patient at highest risk that fracture risk is increased after cessation of denosumab by an order of magnitude which may be too small for being detected when comparing fracture rates between rather small populations. The effects of denosumab withdrawal are insufficiently studied in this patient population. As Gnant's trial is still ongoing, the authors may have a unique opportunity to document the effects of non-renewal of denosumab treatment and to explore measures aimed at preserving bone health after denosumab discontinuation. It must be emphasized that in the present case report, the patient was left without bone protection during approximately 2 months (between February and April 2015) while still on therapy with exemestane. This may have potentiated the effects described above as well as the bone turnover rebound after denosumab withdrawal. For daily practice, this suggests the absence of any window of tolerance during which bone protection may be loosened in patients treated with an AI.

Second, can the increased fracture risk following the rebound in bone resorption after denosumab discontinuation be prevented and if so, how?

In contrast to the transient effects of denosumab on bone turnover, the inhibition of bone resorption and thus the reduction of bone turnover induced by bisphosphonates is long-lasting, with a single intravenous dose of 5 mg zoledronate exerting persisting antiresorptive effects during up to 5 years in osteopenic postmenopausal women [23]. In the Denosumab Adherence Preference Satisfaction (DAPS) study evaluating the adherence to 12 months of treatment with subcutaneous denosumab, 60 mg every 6 months, and 12 months of treatment with oral alendronate, 70 mg once weekly, the rebound of the bone resorption after switching from denosumab to alendronate was at least in part compensated [24]. Thus, the administration of a bisphosphonate as a follow-up treatment to denosumab aimed at preserving the achieved gains in BMD may be further evaluated. However, such regimens have not been developed and no bisphosphonate is approved for use in this indication.

Bone anabolic agents would theoretically shift the balance between bone resorption and coupled bone formation towards the latter, thus allowing for positive bone balance at the remodelling unit level. However, in postmenopausal women with osteoporosis, switching to teriparatide after 24 months of therapy with denosumab resulted in progressive or transient bone loss [25]. Whether a higher dose of teriparatide than 20 μg daily would allow for preservation of bone mass or further BMD increase is unknown. In the same study, 2 years of concomitant treatment with teriparatide and denosumab was superior to either therapy alone in terms of BMD increases [26]. Whether such a combination therapy during adjuvant AI therapy would expose patients to a lesser rebound effect after withdrawal is unknown.

Finally, what is the most appropriate treatment option in the proposed case report?

Due to the lack of data, no evidence-based treatment option is available. Facing the good initial response to denosumab under AI therapy, the multiple fractures following denosumab withdrawal, and following the old adage primum non nocere, treatment with denosumab was resumed.

Conclusions

We hypothesize rebound-associated vertebral fractures to be the clinical manifestation of the rebound phenomenon due to the joined presence of high bone turnover and accumulated fatigue damage after discontinuation of reversible highly potent antiresorptives. Studies are urgently needed to i) prove the underlying pathophysiological processes suggested above, ii) establish the predictive criteria exposing patients to an increased risk of RVF, and iii) determine appropriate treatment regimens to be applied in such patients. Finally, we recommend sharpened post-marketing surveillance awareness for rebound phenomena aimed at minimizing harm after drug discontinuation, especially in the more flexible context of daily practice.

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Compliance with ethical standards The patient gave written informed consent for anonymized case presentation and publication.

Conflict of interest AWP received advisory boards (consulting fees) from Amgen Switzerland; KL received advisory boards (consulting fees) from Amgen, MSD, Eli Lily, and UCB; and none for PhZ.

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