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CASE REPORT

Alendronate after denosumab discontinuation in women previously exposed to bisphosphonates was not effective in preventing the risk of spontaneous multiple vertebral fractures: two case reports

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Abstract

At denosumab discontinuation, an antiresorptive agent is indicated to reduce the high bone turnover, the rapid bone loss, and the risk of spontaneous vertebral fractures. We report two cases of postmenopausal women, previously exposed to bisphosphonates, treated with alendronate at denosumab discontinuation. Alendronate was ineffective to avoid spontaneous clinical vertebral fractures. They presented three and nine spontaneous vertebral fractures 8 and 12 months after denosumab discontinuation, respectively. Ineffectiveness of alendronate was attributed to insufficient control of the rebound as assessed by B-crosslaps measures in the first case, and partially to the high risk of fractures in the later. In both situations, the increased fracture risk may have favoured these new fractures. It is urgent to define effective therapeutic strategies to avoid spontaneous vertebral fractures after denosumab discontinuation.

Introduction

Denosumab reduces bone resorption, increases bone mineral density (BMD), and reduces fracture risk [1]. Denosumab treatment for up to 10 years is associated with low fracture incidence and continued increases in BMD. Denosumab 60 mg twice per year is widely prescribed in women and men with osteoporosis and in patients receiving adjuvant aromatase inhibitors for breast cancer or androgen deprivation therapy for prostate cancer, and for the treatment of glucocorticoid-induced osteoporosis [2]. Denosumab discontinuation induces a rebound effect. B-crosslaps increase above baseline values for 2 years [3]. The increase in lumbar spine and total hip BMD is partially or completely lost within 1 year of denosumab discontinuation [3, 4]. The possible consequences of the rebound in bone turnover markers (BTMs) are the occurrence of multiple clinical spontaneous vertebral fractures (MCSVFs) [5–8]. MCSVFs occur in the 8 to 16 months (median 11) following last denosumab injection, with a mean number of 4.7 VFs per woman [7]. The incidence of MCSVFs depends on follow-up duration and whether or not antiresorptive treatment is prescribed before and/or after denosumab discontinuation [6, 8, 9]. To avoid the rebound effect and MCSVFs, several authors advocate prescribing a potent bisphosphonate after denosumab discontinuation [10–12].

We report the cases of two women, previously exposed to bisphosphonates, who suffered of MCSVFs at denosumab discontinuation despite a preventive treatment with alendronate.

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Case reports

Case 1

This 67-year-old woman was known for osteoporosis, without any fracture, since the age of 53. Her only risk factor was a familial history of densitometric osteoporosis. She took

risedronate for 4 years, and then raloxifene for 6 years. At 63 years, BMD lumbar spine, total hip, and femoral neck T-scores were − 3.6, − 2.5, and − 3.5, respectively, similar to the values obtained at age 53. She received seven doses of denosumab every 6 months until January 2017. In August 2017, BMD lumbar spine, total hip, and femoral neck T-scores were − 3.3, − 2.4, and − 2.5, respectively. Vertebral morphometry confirmed the absence of fracture. According to the wish of the patient, and due to the duration of antiresorptive therapy and the BMD gain, denosumab was discontinued. B-crosslaps (fasting blood sample in the early morning, normal range for premenopausal women 25–573 ng/l) were measured at 146 ng/l in August 2017, 7 months after last denosumab injection; and at 486 ng/l in September 2017 when alendronate 70 mg weekly was started. According to the patient, the treatment was taken carefully weekly and in accordance with the instructions. In early January 2018, B-crosslaps were measured at 1229 ng/l. Due to this biological rebound, a zoledronate infusion was administered mid-January. During this interval, she experienced spontaneous low back pain. MRI revealed T8, T9, and L1 fractures. B-crosslaps measured in early February were at 183 ng/l. Figure 1 describes the evolution of B-crosslaps. In July 2018, BMD lumbar spine, total hip, and femoral neck T-scores were − 3.8, − 2.7 and − 2.7, respectively, with a significant decrease in comparison with August 2017 (Table 1).

Case 2

This 68-year-old woman was known for osteoporosis for 10 years. Her only risk factor was previous T12, L1, and L2 fractures, which had been treated with vertebroplasty. She received oral bisphosphonates (risedronate, ibandronate) for 3 years. Because of T10 fracture, strontium ranelate was introduced for 2.5 years. At 64 years, the treatment was switched to denosumab due to a new fracture in L4. At the onset of denosumab, BMD femoral neck T-score was at − 1.9 (loss of 7.7% in 8 months). She received six doses of denosumab, every 6 months, from June 2014 to January 2017, without fracture during that time. In March 2017, BMD femoral neck T-score was at − 1.5. After 3 years of treatment with a good densitometric response in the osteopenic range and the absence of a new fracture, denosumab was stopped. In July 2017, following the recommendations of the European Calcified Tissue Society [12], alendronate 70 mg weekly was started. According to the patient, the treatment was taken carefully weekly and in accordance with the instructions. Two months later, she experienced spontaneous thoracolumbar pain. MRI revealed acute T5, T6, T8, T9, T11, L3, and L5 fractures (Fig. 2). In January 2018, still under alendronate, a MRI revealed acute T7 fracture and a worsening of the T9 fracture (Fig. 2). In February 2018, BMD femoral neck T-score was − 1.8, showing a loss of 5% (Table 1). B-crosslaps were at 61 ng/l in March 2017, 2 months after last denosumab injection and 438 ng/l in January 2018 (Fig. 1). A broad biological assessment excluded secondary causes of osteoporosis. Due to the clinical severity of the fractures, the failure of alendronate and the absence of biological rebound, anabolic, alendronate were changed to teriparatide in May 2018.

Discussion

These case reports illustrate the difficulty of managing denosumab discontinuation. First, in both cases, alendronate

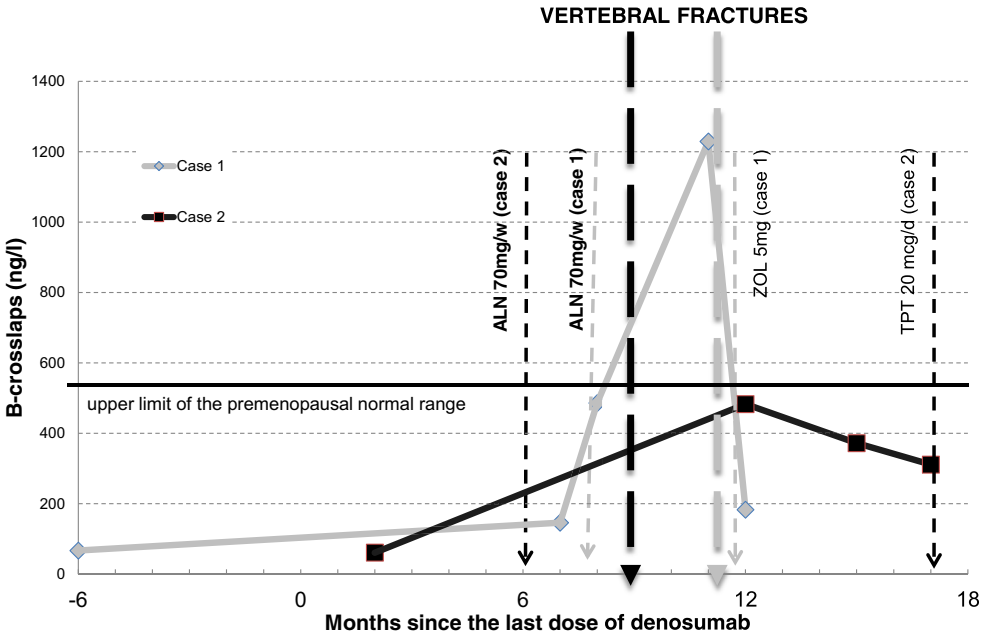

Fig. 1 Evolution of B-crosslaps before and after denosumab discontinuation

Table 1 Evolution of bone mineral density

Case 1	3 y before Dmab	At Dmab initiation	7 m after last Dmab	18 m after last Dmab
LS T-score (SD)	− 3.4	− 3.6	− 3.3	− 3.8
FN T-score (SD)	− 3.3	− 3.5	− 2.5	− 2.7
Case 2	2 y before Dmab	At Dmab initiation	2 m after last Dmab	13 m after last Dmab
LS T-score (SD)	− 1.8	− 2.3	− 1.5	− 1.4
FN T-score (SD)	− 1.4	− 1.9	− 1.5	− 1.8

Dmab denosumab, *FN* femoral neck, *LS* lumbar spine, *m* months, *SD* standard deviation, *y* years

after denosumab discontinuation was ineffective in preventing MCSVFs. Second, B-crosslaps did not allow us to adapt antiresorptive treatment. In case 1, monitoring of B-crosslaps was too distant in time under bisphosphonate treatment; in case 2, a significant increase in B-crosslaps was not evidenced despite the presence of MCSVFs. The highest value of B-crosslaps in the first case was not the consequence of vertebral fractures, since fractures occurred after this measurement. Third, exposure to bisphosphonates prior to denosumab was neither effective in preventing the biologic rebound in case 1 nor MCSVFs in both cases.

After denosumab discontinuation, it is imperative to limit the rebound effect. The first goal is to avoid MCSVFs, the second to limit the bone loss. There is a consensus on the need to administer an antiresorptive treatment after denosumab discontinuation in order to limit the rebound effect [10, 11]. The hypothesis of high bone turnover as a risk factor for MCSVFs is supported by various observations [5, 7, 13, 14]. Nevertheless, some case reports suggest that raloxifene may not be effective in preventing the risk of MCSVFs and that bisphosphonates at usual doses may not be sufficient to avoid bone loss [15, 16]. It is not yet clear how to determine and/or optimize the efficacy of antiresorptive therapies.

One way to quantify the antiresorptive effect of osteoporosis treatments is to measure the BTMs decrease in treated patients. Alendronate 70 mg weekly and intravenous zoledronate 5 mg (4 mg in the pivotal study) are the most powerful bisphosphonates, with a bone resorption markers decrease between 74 and 82% [17, 18]. Since bisphosphonates are deposited on areas of bone resorption, they must probably be given when the rebound effect, measured by BTMs increase, has already begun. This consideration seems of little importance if an oral bisphosphonate is administered repeatedly, but is essential if a single injection of zoledronate is administered [10, 16]. In case 1, B-crosslaps value increased gradually after stopping denosumab, which could be considered as a marker of the rebound effect, and we hoped that alendronate would control it, bone loss would be limited and the risk of MCSVFs avoided. Unfortunately, alendronate administration after denosumab discontinuation was unable to avoid the B-crosslaps increase. Moreover, a sustained BTM decrease is currently not a guarantee for avoiding the risk of MCSVFs (case 2). Thus, a BMD decrease and the occurrence of MCSVFs were observed despite B-crosslaps values remaining within the range of premenopausal

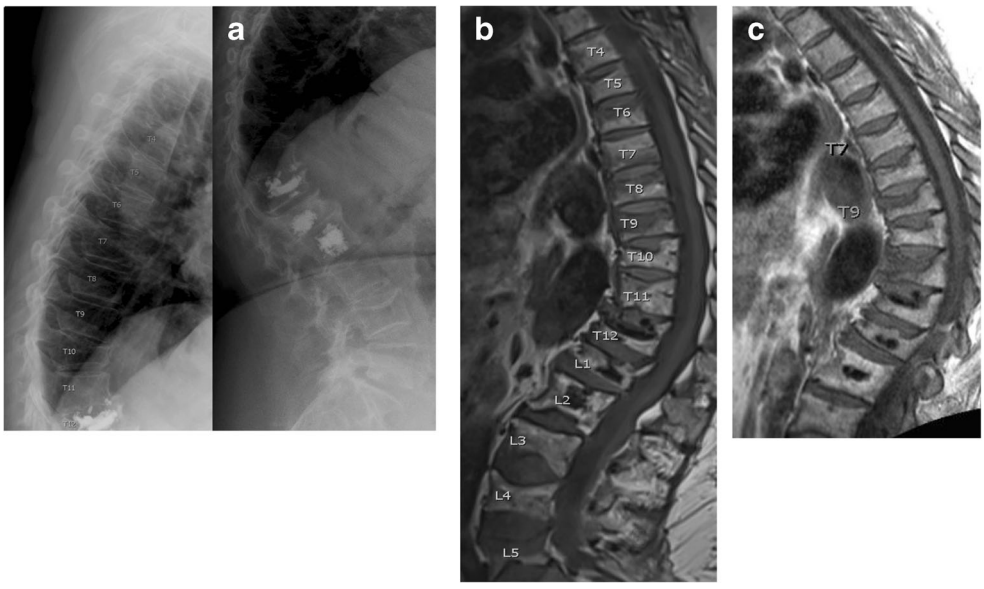

Fig. 2 Case 2. Thoracic and lumbar X-ray prior to denosumab discontinuation (**a**). MRI in T1 sequence 9 (**b**) and 12 (**c**) months after denosumab discontinuation

women. It is possible that in case 1, even though the B-crosslaps were in the normal range for premenopausal women, the rebound was already too important to be inhibited by the progressively absorbed alendronate, i.e., that alendronate was started too late (alendronate was started only when CTX levels had already tripled). Moreover, the alendronate absorption or the compliance may vary from one patient to another and be different from other bisphosphonates. The optimal time-point for B-crosslaps follow-up is not known, and we may presume that the efficacy of alendronate may have been checked earlier. Measurement of BTMs every month or 2 months could be used to assess the effectiveness of antiresorptive therapy, and, if necessary, to replace it or to adjust its dosage. In case 1, zoledronate was more efficacious than alendronate in controlling B-crosslaps. The reasons for the lack of increase of B-crosslaps even in the presence of MCSVFs in case 2 are not known. The evolution of our two cases reaffirms the need to open a debate to determine and optimize the effectiveness of this therapeutic strategy.

Some case reports suggest that the biological rebound effect is reduced in patients treated with bisphosphonates before denosumab initiation [19]. Unfortunately, this strategy does not seem to avoid the risk of MCSVFs [7, 13]. A series of nine postmenopausal women recently demonstrated that prolonged exposure to bisphosphonates (7.4 ± 3.2 years) prior denosumab treatment does not prevent MCSVFs after denosumab discontinuation [13]. However, this study had several methodological issues and its conclusions have been questioned [20, 21]. Our both patients were exposed to oral bisphosphonate prior denosumab treatment, the first one to risedronate for 4 years (6 years before denosumab initiation) and the second one to risedronate and ibandronate for 3 years (2.5 years before denosumab initiation). However, the potential benefit of prior bisphosphonate exposure may differ depending on bisphosphonate, its administration duration, or the delay between the end of bisphosphonate therapy and denosumab initiation. The off-effect upon stopping risedronate or ibandronate is shorter than with alendronate or zoledronate. In both cases, probably no residual effects from these previous treatments should be expected after so many years. Whether the residual effect of a previously given bisphosphonate can be assessed by the evolution of BTMs after denosumab discontinuation has never been analyzed.

Previous VFs have been suggested as risk factor for suffering this clinical event [8]. This may have been a risk factor in case 2; however, the number of new VFs was too high. Moreover, the patient in case 1 had not presented any fracture prior to denosumab. Therefore, the clinical profile of patients who will have MCSVFs after discontinuing denosumab is still unknown. These two cases illustrate the difficulty of managing denosumab discontinuation in the absence of detailed recommendations and/or randomized studies. These cases cannot be generalized, particularly because these women had severe osteoporosis, denosumab duration was probably too short, and compliance with alendronate was not verified by electronic devices.

We conclude that, in these cases, alendronate was not efficacious in preventing the risk of spontaneous vertebral fractures after denosumab discontinuation. These two cases demonstrate that denosumab should not be prematurely discontinued in patients who remain at high risk of fractures. Studies are urgently needed to assess the optimal timing, doses, monitoring, and duration of therapeutic strategies after denosumab discontinuation.

Compliance with ethical standards

Conflict of interest None.

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