ORIGINAL ARTICLE

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Zoledronate for the Prevention of Bone Loss in Women Discontinuing Denosumab Treatment. A Prospective 2-Year Clinical Trial

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ABSTRACT

Cessation of denosumab treatment is associated with increases in bone turnover above baseline values and rapid bone loss. We investigated the efficacy of zoledronate to prevent this bone loss in women with postmenopausal osteoporosis who were treated with denosumab (mean duration 2.2 years) and discontinued treatment after achieving osteopenia. Women were randomized to receive a single 5-mg infusion of zoledronate (ZOL) ($n = 27$) or two additional 60-mg injections of denosumab (Dmab) ($n = 30$). Both groups were followed for a total period of 24 months. At 24 months lumbar spine–bone mineral density (LS-BMD) was not different from baseline in the ZOL group, but decreased in the Dmab group by (mean ± SD) 4.82% ± 0.7% ($p < 0.001$) from the 12-month value; the difference in BMD changes between the two groups, the primary endpoint of the study, was statistically significant ($p = 0.025$). Results of femoral neck (FN)-BMD changes were similar. ZOL infusion was followed by small but significant increases in serum procollagen type 1 N-terminal propeptide (P1NP) and C-terminal telopeptide of type 1 collagen (CTX) during the first year and stabilization thereafter. In the Dmab group, bone turnover marker values did not change during the first 12 months but increased significantly at 15 months and in the majority of women these remained elevated at 24 months. Neither baseline nor 12-month bone turnover marker values were associated with BMD changes in either group of women. In the Dmab group, three patients sustained vertebral fractures (two patients multiple clinical, one patient morphometric) whereas one patient in the ZOL group sustained clinical vertebral fractures 12 months after the infusion. In conclusion, a single intravenous infusion of ZOL given 6 months after the last Dmab injection prevents bone loss for at least 2 years independently of the rate of bone turnover. Follow-up is recommended, because in a few patients ZOL treatment might not have the expected effect at 2 years. © 2019 American Society for Bone and Mineral Research © 2019 American Society for Bone and Mineral Research.

KEY WORDS: BONE MINERAL DENSITY; DENOSUMAB; DISCONTINUATION; OSTEOPOROSIS; VERTEBRAL FRACTURES; ZOLEDRONIC ACID

Introduction

Denosumab (Dmab), a monoclonal antibody against the receptor activator of nuclear factor κB ligand (RANKL), substantially decreases bone resorption and turnover, increases bone mineral density (BMD), and reduces the risk of fractures in women with postmenopausal osteoporosis.[1] Cessation, of treatment, however, is followed by rapid reversal of its favorable skeletal effects, associated in a few patients with multiple vertebral fractures.[2–10] This is attributed to an increase in bone turnover above pretreatment values, a response described as "rebound phenomenon" probably due to upregulation of osteoclastogenesis.[2,3,11] To prevent this sequence of events, it is recommended that patients discontinuing Dmab therapy should be administered bisphosphonates.[8,12,13] These recommendations are mainly based on theoretical considerations of the pharmacodynamics of Dmab and bisphosphonates and limited, inconsistent evidence of clinical studies. Moreover, all recommendations emphasize that an optimal bisphosphonate regimen for patients discontinuing Dmab therapy is currently unknown.

To address this clinically important issue we prospectively investigated the efficacy of a single intravenous infusion of

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zoledronate (ZOL) to prevent bone loss in women with postmenopausal osteoporosis following discontinuation of treatment with Dmab after attaining a non-osteoporotic BMD.

Patients and Methods

Patients

"Zoledronic Acid to Maintain Bone Mass After Denosumab Discontinuation (AfterDmab)" is a 2-year parallel assignment, open label, multicenter, randomized, efficacy study (https://clinicaltrials.gov/ct2/show/NCT02499237). Previously treatment-naïve ambulatory women, ≥50 years old, with postmenopausal osteoporosis who received injections of Dmab every 6 months and achieved non-osteoporotic BMD *T*-scores (> −2.5 and ≤ −1) at the hip or the spine were randomized (1:1) to receive a single 5-mg i.v. infusion of ZOL (given 6 months after the last Dmab injection with a 3-week window) or to continue Dmab and receive two additional injections every 6 months (6-monthly injections). Following either the ZOL infusion or the last Dmab injection, all women received no treatment and were followed until 2 years from randomization. All women were also given vitamin D (cholecalciferol 800 IU/day) and calcium carbonate (500 mg twice per day [b.i.d.]) supplements (Fig. 1). Use of other medications affecting bone metabolism during the last 3 years, a bone disease other than postmenopausal osteoporosis, creatinine clearance <60 mL/min/1.73 m^2, and serum 25-hydroxy vitamin D (25-OHD) concentrations lower than 20 ng/mL (50 nmol/L) were the main exclusion criteria; additional exclusion criteria were any type of cancer, uncontrolled endocrine diseases, and liver failure. Patients were seen in the clinic at baseline and at 6, 12, 15, 18, and 24 months. During these visits pre-dose, fasting morning blood samples for the measurement of bone turnover markers (BTMs) were obtained and stored at −30°C. The design of the study allows for the first time the prospective evaluation of the following endpoints: first, the effect of a single ZOL infusion, given 6 months after the last Dmab injection, on BMD and BTMs in the following 2 years; second, the direct comparison of ZOL with Dmab treatment over 12 months in patients previously treated with Dmab; third, the comparison of the long-term changes of BMD and BTMs following the single ZOL infusion (24 months) or the last Dmab injection (18 months); finally, the assessment of the incidence of multiple vertebral fractures following the discontinuation of Dmab, among patients never treated with any other osteoporosis medication. The study was approved by the local Medical Ethical Committees, and all patients provided written informed consent.

Ethical considerations

At the time the study was designed, available data in a similar population had shown return of BMD to baseline and no clinical vertebral fractures in 128 women up to 2 years following discontinuation of Dmab.[2] This was clearly communicated to the patients and we restricted the follow-up to 1 year after Dmab discontinuation. The study was initiated in 2015 and posted in ClinicalTrials.gov in July 2015. At that time, although bone loss following the discontinuation of Dmab treatment was known, there was no guidance regarding post-Dmab management, especially of patients such as ours who were osteopenic when recruited and received an additional year of treatment after entering the study. The first case reports of multiple vertebral fractures following discontinuation of Dmab were published in 2016. The European Calcified Tissue Society (ECTS) position statement was published in December 2017[12] and the post hoc analysis of the Fracture REduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial followed a few months later.[5] By that time more than one-half of our patients had completed or were near completion of the study. The few

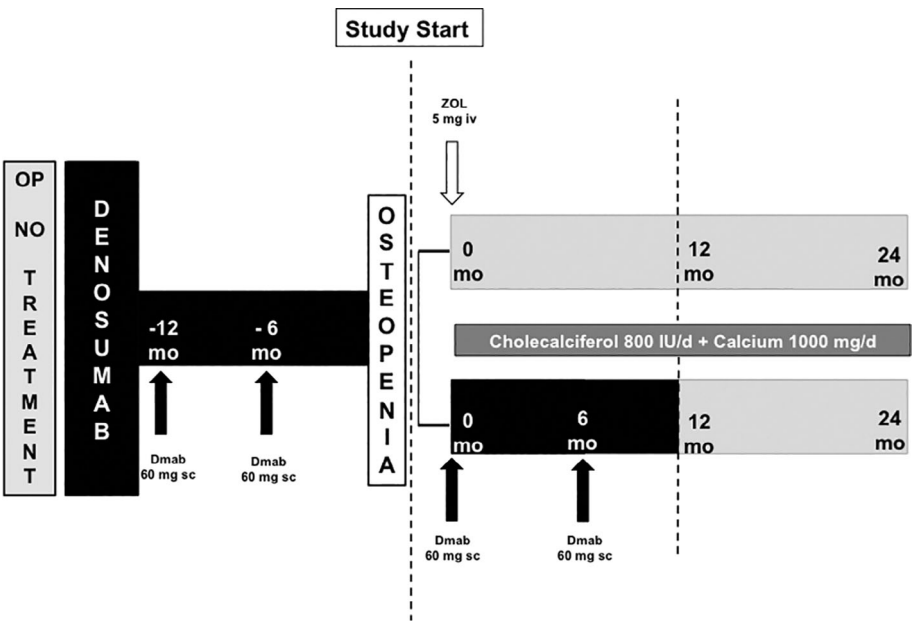

Fig. 1. Design of the study. Black boxes indicate Dmab treatment. ZOL = zoledronate; Dmab = denosumab; i.v. = intravenous; s.c. = subcutaneous; mo = months; OP = osteoporosis.

Table 1. Baseline characteristics of the two groups of women studied

Characteristic	Denosumab (n = 30)	Zoledronate (n = 27)	p
Age (years)	64.8 ± 1.8	65.2 ± 1.7	0.888
Age at menopause (years)	48.9 ± 0.7	47.2 ± 1.0	0.172
BMI (kg/m^2)	27.5 ± 0.7	29.4 ± 0.7	0.063
Height (cm)	157 ± 1	159 ± 1	0.188
Time on denosumab (years)	2.0 ± 0.2	2.4 ± 0.2	0.108
BMD LS (g/cm^2)	0.942 ± 0.009	0.960 ± 0.014	0.278
BMD FN (g/cm^2)	0.799 ± 0.012	0.804 ± 0.016	0.781
T-score LS (SD)	−1.84 ± 0.15	−1.82 ± 0.11	0.608
T-score FN (SD)	−1.68 ± 0.10	−1.59 ± 0.12	0.562
P1NP (ng/mL)	30.3 ± 4.8	24.5 ± 4.8	0.117
CTx (ng/mL)	0.25 ± 0.03	0.20 ± 0.03	0.272
25-hydroxy-vitamin D (ng/mL)	28.9 ± 1.4	28.6 ± 2.3	0.414
Prevalent VFx [n (%)]	5 (16.7)	10 (37.0)	0.081

Data are presented as mean ± SE.

BMD = bone mineral density; BMI = body mass index; CTX = C-terminal telopeptide of type 1 collagen; FN = femoral neck; LS = lumbar spine; P1NP = procollagen type 1 N-terminal propeptide; VFx = vertebral fractures.

who were still in the study were fully informed of this potential risk; however, no one decided to discontinue the study.

Methods

Areal BMD of the lumbar spine (LS; L_1–L_4) and femoral neck (FN) of the nondominant hip were measured at baseline, 12 months, and 24 months by dual energy X-ray absorptiometry (DXA) (Lunar Corporation, Madison, WI, USA) and changes were calculated. We considered least significant changes (LSCs) ≥5% at the LS and ≥4% at the FN as proposed by the International Foundation for Osteoporosis and the National Osteoporosis Foundation USA[14] and applied in studies of discontinuation of bisphosphonate therapy.[15] Lateral radiographs of the spine were also performed annually. All radiographs were examined by a skeletal radiologist who had no knowledge of the patients' treatment assignment. New fractures of previously normal vertebrae were considered those with grade 2 or greater deformity using the Genant semiquantitative method.[16] A worsening of a prevalent vertebral fracture was defined as an increase of one or more grades from baseline. Procollagen type 1 N-terminal propeptide (P1NP), and C-terminal telopeptide of type 1 collagen (CTX) were measured in stored serum samples after the end of the study and samples of individual patients were assayed in the same run. Serum P1NP and CTX were measured by electrochemiluminescence immunoassays "ECLIA" on a Cobase 411 analyzer (Roche Diagnostics, Mannheim, Germany) (P1NP intraassay coefficient of variation (CV) ≤2.3%, interassay CV ≤3.0%; CTX intraassay CV ≤2.5%, interassay CV ≤4.6%; upper limit of normal range for postmenopausal women, P1NP 76 ng/mL, CTX 1.0 ng/mL, and for premenopausal women, 56 ng/mL and 0.57 ng/mL, respectively.

Treatment outcomes

The primary endpoint of the study was the difference in LS-BMD changes between the two groups from 12 to 24 months. Secondary endpoints included: the difference in FN-BMD changes between the two groups from 12 to 24 months; the difference in LS-BMD and FN-BMD changes between the two groups at 12 months; the differences in serum BTM levels between the two groups throughout the study and the relationship between serum BTM levels and BMD changes. The difference in LS-BMD and FN-BMD changes between the two groups 24 and 12 months after discontinuation (6 months after the last injection) of Dmab for the ZOL and Dmab groups, respectively, and the incidence of new vertebral fractures (clinical and morphometric) and other fragility fractures were exploratory endpoints.

Statistical analysis

The trial required 56 patients to have a power of 95% to detect a 6% difference in LS-BMD between the two treatment groups with a two-sided error α probability of 0.05. Data for continuous variables are presented as mean ± standard error of the mean (SE). Data for categorical variables are presented as number and/or frequencies. The Kolmogorov-Smirnov test was used to test the normality of distribution of continuous variables. Within-group comparisons of continuous variables were performed with repeated measures analysis of variance (ANOVA) or Friedman test. In case of statistically significant trend, multiple pairwise comparisons were performed with Bonferroni post hoc adjustment. Independent t test or Mann-Whitney test were used to compare continuous variables between groups. Chi-square or Fischer's exact test were used for comparisons of categorical variables between groups. Spearman's (rs) coefficient of correlation was used for bivariate correlations between continuous variables. Analysis of primary efficacy endpoint was by intention-to-treat; missing values were handled with the last-observation-carried-forward method. A two-sided p value of <0.05 was considered statistically significant in all the above tests. Statistical analysis was performed with SPSS for Macintosh, version 21.0 (IBM Corporation, Armonk, New York, USA).

Results

Between May 2015 and October 2016 we invited 71 consecutive women fulfilling the inclusion criteria to participate in the study, of whom 11 declined participation. The remaining 60 women were randomly assigned (1:1) to continue Dmab or to receive ZOL; of the latter, three women withdrew their consent before the start of the study and did not receive treatment. Thus, 30 women received Dmab and 27 ZOL. The ZOL infusion was administered at 6.5 ± 0.1 months after the last Dmab injection (7–19 days after the expected date of the following Dmab

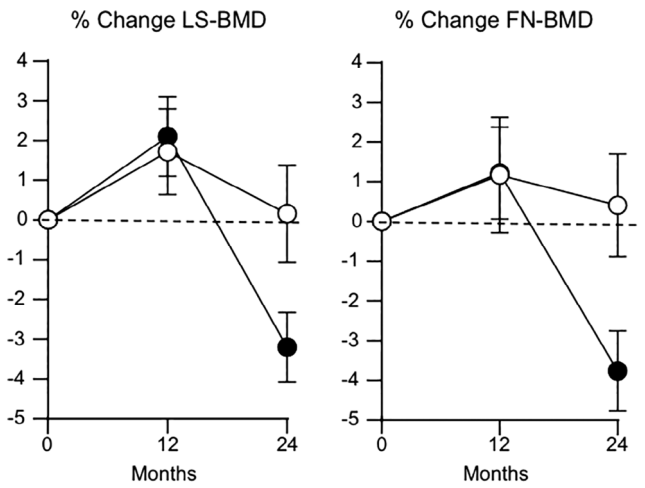

Fig. 2. Percent changes (mean ± SE) in LS-BMD (left panel) and FN-BMD (right panel) from baseline in women treated with ZOL (open circles) and Dmab (closed circles).

injection). Three women discontinued the study: one in each group following clinical vertebral fractures, and one in the Dmab group withdrew her consent.

Baseline clinical, radiological, and biochemical characteristics were similar between the two groups (Table 1). Mean age was 64.8 and 65.2 years, respectively, duration of previous Dmab therapy was similar in the two groups (1 to 4 years for both), and mean duration of Dmab treatment was 2.0 and 2.4 years in the Dmab and ZOL groups, respectively (Table 1). More patients in the ZOL group had prevalent vertebral fractures but the difference with the Dmab group was not statistically significant.

BMD

Changes in LS-BMD and FN-BMD during the study are shown in Fig. 2 and Table 2. Compared to baseline, LS-BMD increased, but not significantly, in both groups at 12 months (ZOL 1.7% ± 1.1%, $p = 0.384$; Dmab 2.1% ± 1.0%, $p = 0.150$). The difference in LS-BMD increases between the two groups was also not significant ($p = 0.643$). At 24 months LS-BMD returned to baseline in the ZOL group (compared to baseline: 0.1% ± 1.2%; $p = 0.203$), but decreased significantly in the Dmab group by 4.82% ± 0.7% ($p < 0.001$) from the 12-month value, reaching values that were also significantly ($p = 0.021$) lower than the baseline values. The difference of LS-BMD changes between the two groups from month 12 to month 24, the primary outcome of the study, was significant ($p = 0.025$), as was also the difference in changes of FN-BMD ($p = 0.005$) (Fig. 2, Table 2).

The differences in BMD changes between the two groups 24 and 12 months after discontinuation of Dmab (6 months after the last injection) for the ZOL and Dmab group, respectively, were also statistically significant both at the LS-BMD ($p = 0.003$) and the FN-BMD ($p = 0.007$) (Table 2).

There was no relationship between the number of Dmab injections and LS-BMD changes (month 12 to 24) in either group of women; in the Dmab group, the correlation coefficient (*rs*) between changes in LS-BMD and number of denosumab injections (4 to 10) was −0.155 ($p = 0.415$). In the ZOL group, the respective *rs* was −0.002 ($p = 0.991$).

However, responses of individual patients to ZOL were variable (Fig. 3A and 3B) and in three women decreases of LS-BMD greater than the LSC were observed at 24 months (Fig. 3B); in four women FN-BMD loss exceeded LSC.

BTMs

Results of BTM measurements during the whole study are depicted in Fig. 4 and Supplementary Table 1. At study entry (6 months after the last prestudy Dmab injection) serum P1NP levels were above the upper limit of the reference range in four patients (three above postmenopausal and one above premenopausal values); no patient had serum CTX values above postmenopausal reference range, but in four patients values were above the upper limit of normal of the premenopausal range. The ZOL infusion was followed by a small but significant increase in serum CTX and P1NP values during the first year and stabilization thereafter. At 24 months, serum P1NP levels were above the upper limit of normal postmenopausal values in two patients (7.4%) and in another five patients these were above the premenopausal reference range. Serum CTX values at 24 months were increased (premenopausal range) in two patients (Supplementary Table 2). Thus, a single ZOL infusion, though highly efficacious, could not completely retain BTM levels within the reference range (either premenopausal or postmenopausal) following Dmab discontinuation over 2 years. In patients treated with Dmab, there was no change in mean values of both BTMs during the first 12 months and no patient had serum values above the upper limit of the reference ranges. At month 15 (9 months after the last Dmab injection) serum P1NP and CTX values increased significantly, reaching levels that were also significantly higher than

Table 2. Comparisons of BMD changes between groups

Variable	Change	Denosumab group	Zoledronate group	*p* (between groups)
BMD LS (g/cm^2)	Baseline to month 12	0.019 ± 0.009	0.016 ± 0.010	0.643
	Month 12 to month 24	−0.045 ± 0.007	−0.018 ± 0.009	0.025
	6 months after the last Dmab injection[1]	−0.045 ± 0.007	−0.002 ± 0.012	0.003
BMD FN (g/cm^2)	Baseline to month 12	0.009 ± 0.009	0.001 ± 0.011	0.561
	Month 12 to month 24	−0.038 ± 0.007	−0.004 ± 0.009	0.005
	6 months after the last Dmab injection[1]	−0.038 ± 0.007	−0.004 ± 0.010	0.007

Data are presented as mean ± SE.

BMD = bone mineral density; FN = femoral neck; LS = lumbar spine.

[1] This comparison addresses the evaluation of our exploratory endpoint, which was the difference in LS-BMD and FN-BMD changes between the two groups after discontinuation (6 months after the last injection) of Dmab. According to the design of the study this refers to the change from baseline to month 24 for the ZOL group, whereas for the Dmab group this refers to the change from month 12 to month 24.

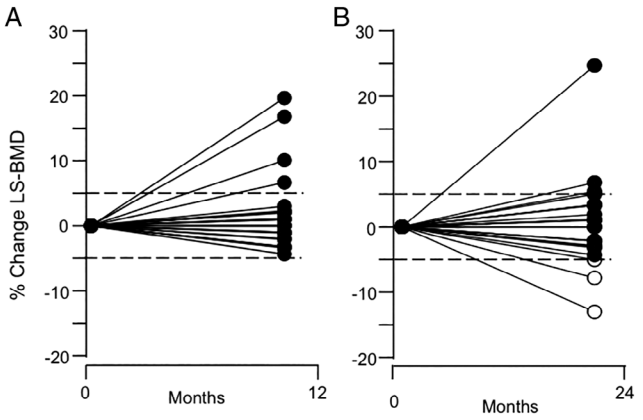

Fig. 3. Percent changes of LS-BMD in individual patients treated with zoledronate 5 mg i.v. at baseline (month 0) at 12 months (*A*) and 24 months (*B*). Dashed lines = LSC ≥5%; open circles = patients with LSC >5%. LSC = least significant change.

those of the ZOL group. At 24 months only two patients had serum P1NP values within the premenopausal range; serum CTX values within this range were measured in 12 patients. Thus, independently of the definition of the reference range, high levels of BTMs persisted 18 months after the last Dmab injection in the majority of studied patients.

Relationships between serum BTMs values and BMD changes

Neither baseline nor 12-month values of BTMs were associated with changes in BMD in either group of women during the whole study. Particularly important for clinical practice was the lack of a relationship in ZOL-treated women (Supplementary Fig. 1); even when women were divided according to baseline median BTM values (below or above) there was no significant difference in BMD changes at 12 or 24 months between the two subgroups (*p* values between 0.1 and 0.895 for all BMD measurements for both serum P1NP and CTX).

In Fig. 5, individual changes in LS-BMD (12 to 24 months) above or below the LSC in women treated with Dmab are shown together with age, number of Dmab injections, and BTM values. There was no significant difference in any of these parameters between patients with bone loss ≥5% compared with those with bone loss <5%. The results of these analyses combined, indicate that BMD changes following either a ZOL infusion or discontinuation of Dmab cannot be predicted by BTMs or any other of the clinical characteristics assessed.

Fractures

During the study three patients sustained clinical vertebral fractures, one in the ZOL group (3.7%) and two in the Dmab group (6.7%). In the first patient, these occurred 12 months after the ZOL infusion—18 months after the last Dmab injection—(one new and one worsening of a preexisting vertebral deformity); in the other two patients, these occurred 9 and 12 months after the last Dmab injection and consisted of one new and worsening of two prevalent vertebral deformities in the first patient and one new and one worsening in the second patient. In the ZOL-treated patient the vertebral fractures were associated with profound loss of hip BMD at 12 months that was not related to increases in BTMs above the upper limit of normal of premenopausal values, immobilization, or a previously unrecognized, underlying disease (Supplementary Fig. 2). In addition, in an asymptomatic patient with a prevalent vertebral fracture in the Dmab group, a new morphometric vertebral fracture was observed on spine radiographs at 24 months. Both groups of patients lost height during the study (Dmab group 2 cm, ZOL group 1 cm), but the difference between them was not significant. Except for a fracture of the fifth metatarsal bone that occurred 17 months after the last Dmab injection in a patient without prevalent fractures, no other nonvertebral fractures were observed in either group of patients during the study.

Adverse events

Eighteen (66.7%) of the 27 women in the ZOL group developed symptoms compatible with a transient acute phase reaction that was treated with paracetamol. No adverse events were recorded in the Dmab group of women. No cases of osteonecrosis of the jaw or atypical femoral fracture were observed.

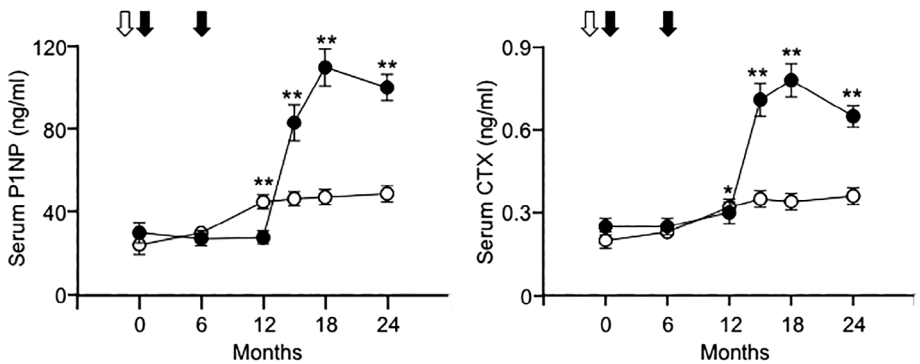

Fig. 4. Serum P1NP (left panel) and CTX (right panel) values during the study. Closed circles = denosumab; open circles = zoledronate; open arrow = zoledronate 5 mg i.v.; closed arrows = denosumab 60 mg s.c. *Significantly different from baseline. **Significantly different from baseline and between groups. Specific *p* values at different time points are shown in Supplementary Table 1.

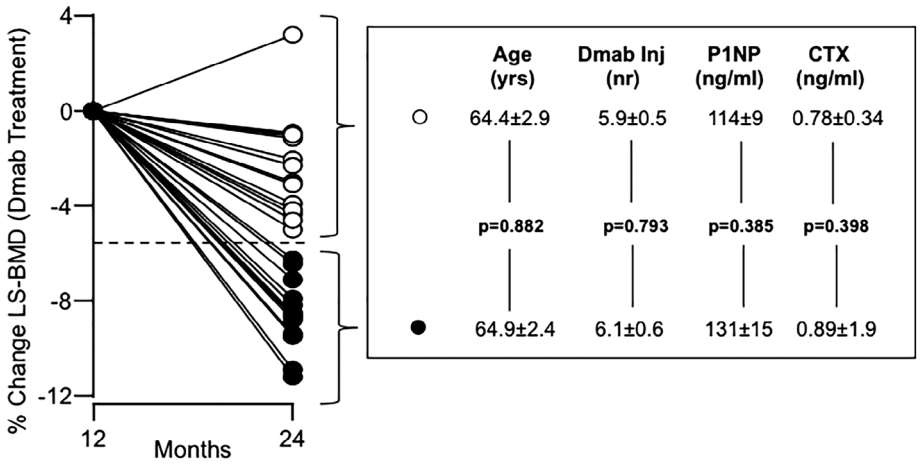

Fig. 5. Percent changes of LS-BMD, above or below LSC (dashed line), between 12 and 24 months in individual patients treated with denosumab 60 mg s.c. Open circles = patients with changes <5%; closed circles = patients with decreases ≥5%. Means±SE are shown for all studied parameters; for bone turnover markers the highest values observed are shown. Dmab = denosumab, inj = injections, nr = number of injections (total: before and during the study).

Discussion

In recent years the availability of potent therapeutic agents that can induce large increases in BMD initiated discussions about the possibility to apply treat-to-target or goal-directed strategies in the management of patients with osteoporosis.[17–22] Although the definition of specific targets is still being debated, it is generally agreed that attainment of non-osteoporotic BMD values could be one such target. In the FREEDOM study and its Extension, Dmab was shown to increase BMD to such levels in a substantial number of women with postmenopausal osteoporosis[22,23] that might lead in clinical practice to treatment discontinuation when the target is reached. However, the effect of Dmab, as of other antiosteoporotic medications with the exception of bisphosphonates, is rapidly reversible and may be also associated in a few patients with increased incidence of clinical vertebral fractures.[2–10] A strategy to consolidate and maintain the Dmab-induced BMD gains for longer periods of time is, therefore, desirable.

We show here that a single 5-mg i.v. infusion of ZOL given 6 months after the last injection of Dmab therapy maintains BMD at the spine and the hip in women with non-osteoporotic BMD for 1 year and in most of them for 2 years. The efficacy of ZOL to preserve BMD gains from Dmab treatment given for 2 to 7 years to women with osteoporosis was previously examined in case series.[24–27] In these reports responses to ZOL were variable and ranged from small BMD losses to complete reversal of the gains of Dmab therapy. The efficacy of oral bisphosphonates to prevent bone loss following Dmab discontinuation has also been examined in studies of different duration and designs. A study of 250 postmenopausal women with BMD *T*-scores between −4 and −2 who received 1 year of Dmab followed by 1 year oral alendronate showed maintenance of BMD associated with lack of rebound of BTMs.[28] Notably, in a case series of five postmenopausal women, who received risedronate 35 mg/week for 1 year following cessation of Dmab, lost about one-half of their BMD gains,[26] whereas five women on oral bisphosphonates following discontinuation of Dmab in a phase 2 study showed smaller BMD decreases compared with those who did not receive any treatment.[3] Thus, although it is currently recommended to continue treatment of patients discontinuing Dmab with antiresorptive agents, the evidence supporting this recommendation is not robust. Duration of Dmab treatment, other previous treatments, baseline BMD, as well as time of ZOL administration following cessation of Dmab and/or of BMD measurements have been suggested to contribute to the reported responses. Our study, apart from showing the efficacy of ZOL in preventing bone loss following Dmab discontinuation in osteopenic postmenopausal women, allowed the prospective evaluation of suggested modulators of the response to this bisphosphonate.

Conventional thinking and studies with antiresorptive agents demonstrating greater increases in BMD in patients with higher rates of bone turnover[29,30] support the notion that ZOL might have a better effect on BMD if bone remodeling is not decreased. In line with these considerations, Horne and colleagues[26] suggested that delaying administration of ZOL when transitioning from Dmab, for longer than 6 months may increase the extent of maintenance of BMD gains, a suggestion also supported from limited data obtained in the observation period of the 4-year Denosumab And Teriparatide Administration (DATA) study.[13,31] These arguments might impact clinical practice because they could lead to arbitrary choices of the timing of ZOL administration or to repeated measurements of BTMs until a, yet unspecified, rise of BTMs is documented. We show here that the variability of BMD changes following ZOL treatment is not related to the rate of bone turnover at the time of the infusion or at any other time point assessed during treatment. There is, therefore, no reason to delay the administration of ZOL beyond 6 months after the last Dmab injection. Length of previous Dmab treatment, or number of injections, has also been suggested as contributing factor to the ZOL response.[32] In our study there was no association between BMD responses and number of Dmab injections in either group of patients. Moreover, McClung and colleagues[3] reported that the loss of BMD following discontinuation of Dmab given for 8 or 4 years was practically the same, and Cummings and colleagues[5] found no association between duration of Dmab treatment and incidence of vertebral fractures.

We observed, however, a significant variability in individual BMD responses to ZOL especially at 2 years when three of 27 patients experienced decreases in LS-BMD greater than the LSC that could not be explained either by the timing of the infusion, baseline rate of bone turnover, or baseline BMD. It appears that intrinsic factors, which still need to be defined, may affect the response of a few individuals, as illustrated in our patient with clinical vertebral fractures associated with significant, currently unexplained, decreases of BMD that could not be prevented by the ZOL infusion. In clinical practice it is therefore advisable to measure BMD at 12 months after the ZOL infusion and decide whether additional treatment may be required in a few patients, as also recently suggested.[32]

Our study provided also the opportunity to compare for the first time the effect of a single infusion of ZOL 5 mg with Dmab 60 mg s.c. every 6 months for 1 year in patients previously treated with this agent. Earlier studies of similar design in bisphosphonate-treated women with postmenopausal osteoporosis reported increases in BMD after 12 months with both agents. Dmab induced generally greater increases than ZOL the magnitude of which might depend on the length and type of bisphosphonate pretreatment.[33–35] Our results in Dmab-treated women are similar to those of bisphosphonate-treated women in showing larger increases in LS-BMD with Dmab compared with ZOL which were not, however, statistically significant.

Initial changes in BTM values observed in our study were consistent with the greater potency of Dmab in decreasing bone turnover[34,35] as well as with the pattern of BTM changes observed after a single ZOL infusion to osteopenic women.[36,37] Furthermore, the pattern of increases in BTMs, following discontinuation of Dmab without any follow-up treatment, was as described.[2] These changes of BTMs were not, however, associated with the observed changes in BMD in either group of patients. In a substantial number of women in the Dmab group BTMs were still above the upper limit of normal of the postmenopausal range 18 months after the last Dmab injection but also in 7.4% of patients treated with ZOL at 2 years. Whether in the latter patients BTMs were also increased before the start of Dmab treatment, as is known to occur in some patients with osteoporosis,[38] or are due to a prolonged effect of Dmab withdrawal on bone metabolism that could not be prevented by ZOL, is not known because pretreatment data were not available.

The incidence of all vertebral fractures following discontinuation of treatment in the Dmab group was 10% and that of multiple clinical vertebral fractures was 6.7%. Despite the small number of prospectively studied patients, this incidence is remarkably similar to that observed during 1 year observational follow-up of 65 women treated with Dmab in a phase 2 study (7.7%).[3] These results together with those of the post hoc analysis of the FREEDOM trial and its Extension[1,5] indicate that the frequency of this event is low, as also recently reported in a large retrospective study.[39] Notably, in the study of Bone and colleagues[2] no clinical vertebral fractures were reported in 128 osteopenic women following discontinuation of Dmab after treatment for 2 years. One clinical vertebral fracture was also observed in a patient treated with ZOL 12 months after the infusion (3.7%); in the study of McClung and colleagues[3] one of 17 patients (5.9%) patients who received other antiosteoporotic treatments following discontinuation of Dmab sustained multiple vertebral fractures on risedronate treatment. In contrast, in an RCT of 180 postmenopausal women with osteopenia treated with single ZOL infusions of 1 mg, 2.5 mg, or 5 mg, no clinical vertebral fractures were reported.[36] Moreover, the incidence of clinical vertebral fractures was about 1% 12 months after a 5-mg infusion of ZOL in patients at high fracture risk following hip fracture repair.[40] Obviously the low numbers and different designs do not allow comparisons between studies and it is not possible to confirm or refute a causal link to Dmab pretreatment in our patient who sustained one new fracture and one worsening of a preexisting vertebral deformity after ZOL administration. Importantly, however, all four patients with vertebral fractures (three clinical, one morphometric) in our study had prevalent vertebral fractures grade 2 or greater. Prevalent vertebral fractures have been previously reported as the most important risk factor for clinical vertebral fractures following cessation of Dmab therapy,[5] strongly suggesting that spine X-rays should be performed in all patients in whom discontinuation of Dmab treatment is considered.

Limitations of our study include the small number of treated women, the open label design, and the relatively short duration of Dmab treatment in ZOL-treated patients. This duration of treatment is, however, consistent with "real-world" findings showing adherence to Dmab treatment for 2 years in about 50% of patients in most studies,[41–45] though higher rates have also been reported.[46] In addition, the relatively small number of patients of our study allowed detailed analysis of individual responses, not generally available in large trials, which provided information important for clinical care.

In conclusion, in most women with postmenopausal osteoporosis treated with Dmab in whom discontinuation of treatment is considered when a non-osteoporotic BMD is achieved, a single intravenous infusion of ZOL 5 mg given 6 months after the last Dmab injection prevents bone loss for at least 2 years independent of the rate of bone turnover. Follow-up is recommended, because in a few patients treatment might not have the expected effect at 2 years for currently unknown reasons.

Disclosures

ADA has received lecture fees from Amgen, Eli-Lilly, ELPEN, ITF Hellas, and VIANEX; SEP has received consulting/speaking fees from Amgen, Axsome, Gador, Radius Health, and UCB; SAP has nothing to declare; NMA-D has participated in the Dutch denosumab advisory board and has received research grants from Amgen; PM has received lecture fees and research grants from Amgen; and has received lecture fees from Glaxo, Lilly, Pfizer, Leo, Genesis, ELPEN, VIANEX, and Rafarm.

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