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ORIGINAL ARTICLE

Treatment with zoledronic acid subsequent to odanacatib prevents bone loss in postmenopausal women with osteoporosis

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Abstract

Summary Treatment with zoledronic acid 5 mg maintained bone turnover markers in the premenopausal range, increased lumbar spine bone mineral density, and maintained hip bone mineral density in women previously treated with odanacatib 50 mg weekly.

Introduction The development of odanacatib (ODN), a cathepsin K inhibitor, for treatment of osteoporosis was discontinued due to an increased risk of cardiovascular events. As the treatment is considered reversible, participants from the LOFT trial in Aarhus, Denmark, were offered treatment with zoledronic acid (ZOL).

Methods Sixty-seven postmenopausal women were treated with ZOL 5 mg and followed for 12 months. Of these, 39 had received ODN for 7 years and 28 had received placebo for 5 years and ODN for 2 years. Bone turnover markers (BTM) were measured 3, 6, and 12 months after ZOL, and DXA of spine and hip were performed at time of ZOL treatment and after 12 months.

Results Within the entire study population, BMD at the lumbar spine increased by 2.8 ± 0.9% (mean ± SEM) ($p < 0.01$) from baseline to month 12. There was no significant change in BMD at the total hip ($p = 0.17$) or femoral neck ($p = 0.39$). There was no difference in the changes in BMD from baseline to 12 months between the two groups at any site ($p \geq 0.20$ for all). CTX increased by 107 ± 9% ($p < 0.001$), PINP by 102 ± 16% ($p < 0.001$), osteocalcin by 32 ± 6% ($p = 0.001$) and BSAP by 79 ± 37% ($p = 0.001$) between 3 and 12 months after ZOL. At month 12, BTM were still within the premenopausal reference range. S-25-hydroxyvitamin D increased ($p = 0.059$), while PTH ($p = 0.007$) and eGFR ($p = 0.014$) decreased during the year following ZOL administration.

Conclusion Treatment with ZOL 5 mg maintained BTMs in the premenopausal range and prevented bone loss in women previously treated with ODN.

Keywords Bone turnover markers · Cathepsin K inhibitor · Odanacatib · Osteoporosis · Zoledronic acid

Introduction

Odanacatib (ODN) is an anti-resorptive agent that selectively inhibits cathepsin K, the primary osteoclast (OC)-produced enzyme involved in the degradation of type I collagen and other bone matrix proteins [1]. In a large randomized, placebo-controlled phase III study (the Long-term Odanacatib Fracture Trial, LOFT) treatment with ODN 50 mg weekly for 5 years increased bone mineral density (BMD) at both the lumbar spine (11.2%, $p < 0.001$) and total hip (9.5%, $p < 0.001$) and significantly reduced fracture risk compared to placebo [2]. In the extension trial, all the participants were treated with ODN 50 mg weekly. However, due to an imbalance in the number of strokes with slightly more events among the participants treated with ODN [3], further development of the drug was discontinued in September 2016 (Merck Newsroom Home: http://www.mrknewsroom.com, on September 2, 2016 7:00 am ECT).

At present, the two most widely used anti-resorptive agents are bisphosphonates and denosumab (DMAB). Bisphosphonates induce apoptosis of the osteoclast [4], whereas DMAB is an antibody against receptor-activator of nuclear factor kappa-B ligand (RANKL) that prevents recruitment and differentiation of osteoclasts [5]. Bisphosphonates adhere very strongly to bone with a half-life of several years

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[6] and can therefore often be discontinued after a number of years of treatment while still preserving the anti-fracture efficacy [7, 8]. In contrast, treatment with DMAB is reversible and discontinuation markedly increases bone turnover and probably fracture risk [9–12]. In addition, preliminary evidence suggests that a switch to intra-venous bisphosphonates after DMAB does not maintain BMD [13–15]. This suggests that discontinuation of a reversible anti-resorptive agent (whether it be followed by another anti-resorptive agent or not) is troublesome.

Treatment with ODN suppresses bone turnover and discontinuation markedly increases bone turnover markers above baseline values [16, 17] similar to discontinuation with DMAB. Case series and the FREEDOM study have described multiple vertebral fractures in women discontinuing DMAB [12, 18–20], and similarly, a case report from 2018 describes vertebral fractures in a female participant from the LOFT trial discontinuing ODN [21]. Treatment with ODN is reversible. Unlike DMAB, however, ODN does not affect OC viability, and it is assumed that the increased resorption activity seen after stopping ODN is caused by a compensatory increase in the number of OC producing cathepsin K, which function is no longer inhibited [22]. In addition, the suppression of bone turnover seen with ODN is not as marked as that seen with DMAB [16, 17]. One can therefore speculate that the rebound phase seen after discontinuation of ODN is different from that seen with DMAB and that it may be prevented by administration of bisphosphonates.

In the present follow-up study, we therefore investigated the effect of a single infusion of ZOL after stopping treatment with ODN in postmenopausal women with osteoporosis. The aim of the study was to evaluate changes in BMD and biochemical markers of bone turnover during the 12 months following administration of ZOL. Despite the fact that the development of ODN was discontinued in 2016, the present follow-up study may still provide valuable information about how the different mechanisms of action of reversible anti-resorptive treatments affect the post-treatment outcome and the possibilities of limiting the unwanted effects of reversibility.

Methods

The study population and methods of the LOFT study and the extension study have already been described and published elsewhere [3]. Patients who participated in the LOFT and the LOFT extension trial ($n = 67$) at our research facility in Aarhus, Denmark were offered an infusion of 5 mg zoledronic acid at completion of the LOFT extension trial (baseline) to prevent the potential bone loss associated with discontinuation of ODN. Twenty-eight women had received placebo for the 5 years of the LOFT trial and ODN 50 mg weekly during the LOFT extension trial (PCB-ODN group), and 39 women had received ODN 50 mg throughout the LOFT and the LOFT extension trial periods (ODN-ODN group). In addition, we advised all patients to secure a daily intake of 1000 mg calcium and 20–40 μg vitamin D. To evaluate the effect of ZOL, we performed dual-energy x-ray absorptiometry (DXA) of the lumbar spine (L1–L4) and total hip at baseline and after 12 months using a Hologic Discovery scanner (Hologic, Inc., Waltham, MA, USA). We measured procollagen type I N-terminal propeptide (PINP), C-terminal collagen crosslinks (CTX), osteocalcin, bone-specific alkaline phosphatase (BSAP), parathyroid hormone (PTH), 25-hydroxyvmitamin D, ionized calcium, and estimated glomerular filtration rate (eGFR) 3, 6, and 12 months after administration of ZOL.

The Central Denmark Region Committees on Health Research Ethics have determined that According to the Consolidation Act on Research Ethics Review of Health Research Projects, Consolidation Act number 1083 of 15 September 2017 section 14 (1) only the Committees should only be notified about health research studies. Since the study was not a health research study, The Central Denmark Region Committees on Health Research Ethics was not notified. The Danish Data Protection Agency and The Danish Patient Safety Authority approved the publication.

Statistical analysis

We compared baseline characteristics and percent changes in BMD at month 12 between women treated with PCB-ODN and women treated with ODN-ODN using independent samples *t* test. We assessed normality using quantile-quantile plots (QQ plots). In addition, we adjusted change in BMD for change in PTH and vitamin D using analysis of covariance. We evaluated within-group percent changes in BMD from baseline to 12 months using paired-samples *t* test. We checked the assumptions by plotting the difference in BMD at baseline and after 12 months against the average BMD (Bland–Altman plot) and by a QQ plot of the difference. We adjusted within-group change in BMD for change in PTH and vitamin D using linear regression.

Regarding changes in the biochemical markers over time, we used a mixed model analysis of variance with repeated measures. In the model, the fixed factors were treatment group and time, the repeated measure was time, and the dependent variables were biochemical markers. First, we performed a full-factorial analysis comprising all main effects as well as the interaction between treatment group and time, and next, we removed all non-significant interactions in order to evaluate only the main effects of time and treatment group. We checked for normality using QQ plots of the residuals. In case data were not normally distributed, we log-transformed data (P1NP) and if normality could still not be obtained, we used Friedman's test (eGFR and CTX). For explorative analyses, we adjusted these results for PTH and vitamin D levels having PTH and vitamin D as covariates in the analyses described

above. We performed all analyses using SPSS and level of significance was 0.05.

Results

Sixty-seven postmenopausal women with a mean age of 78 (range 72–90) years participated in this follow-up study. The ODN-ODN group comprised 39 women who had been treated for approximately 7 years with ODN 50 mg weekly and the PCB-ODN comprised 28 women who had been treated with PCB for 5 years and ODN for approximately 2 years. All the participants received ODN treatment for the last 2 years of the LOFT extension study. At baseline, participants in the two treatment groups were well balanced regarding age, body composition, and BMD (Table 1). Three women were lost to follow-up; one patient was excluded from further analysis due to primary hyperparathyroidism, one patient declined further visits at our clinic shortly after treatment with ZOL, and one patient died (cause of death was unrelated to the trial). Five participants refrained from blood samples, thus only had DXA performed at baseline and after 12 months.

Bone mineral density

Changes in BMD are shown in Fig. 1. Within the entire study population, there was a significant increase in lumbar spine BMD (LSBMD) of 2.75 ± 0.92% (mean ± SEM) ($p < 0.01$) from baseline to month 12. There was no significant difference in BMD at the total hip (THBMD) ($p = 0.17$) or femoral neck (FNBMD) ($p = 0.39$).

There were no differences in the changes in BMD from baseline to month 12 between the two groups at the LSBMD ($p = 0.20$), THBMD ($p = 0.22$), or FNBMD ($p = 0.44$). Within the ODN-ODN group, LSBMD also increased significantly from baseline to month 12 by 1.79 ± 0.50% ($p < 0.01$) whereas this change was only borderline significant in the placebo-ODN group (4.25 ± 2.23%, $p = 0.054$). There were no significant differences in changes in BMD from baseline to month 12 in the FNBMD or THBMD in participants in the ODN-ODN group (THBMD $p = 0.06$, FNBMD $p = 0.25$) or in the PCB-ODN group (THBMD $p = 0.77$, FNBMD $p = 0.92$).

Biochemical parameters

Biochemical markers of bone turnover and calcium metabolism were not measured at baseline in this study as these were collected as part of the final visit in LOFT. It was later decided not to analyze these markers at the final visit and they are therefore not available. There was no interaction between treatment groups (ODN-ODN or PCB-ODN) and time for any biochemical marker ($p > 0.40$ for all) meaning that the change in biochemical markers over time was the same in both groups. PTH was significantly lower in the PCB-ODN group compared to the ODN-ODN group ($p = 0.016$) (Fig. 2). For the rest of the biochemical markers there was no difference between the two treatment groups ($p > 0.12$ for all).

The bone resorption marker CTX increased significantly by 107 ± 9% ($p < 0.001$) from month 3 to 12, but remained low and within the reference interval for premenopausal women during the entire study period (Fig. 3). Similarly, PINP, a marker of bone formation, remained low within the reference interval from month 3 to 12 despite a significant increase by 102 ± 16% ($p < 0.001$) (Fig. 4). Similarly, osteocalcin and BSAP increased significantly by 32 ± 6% ($p = 0.001$) and 79 ± 37% ($p = 0.001$), respectively.

PTH, 25-hydroxyvmitamin D, ionized calcium, and eGFR all had mean values within the reference interval during the entire study period (Table 2). 25-Hydroxyvmitamin D increased by 12 ± 3% ($p = 0.059$) and PTH and eGFR both decreased by − 14 ± 3% ($p = 0.007$) and − 3 ± 1% ($p = 0.014$), respectively.

Fracture assessment

Three patients suffered a fracture during the follow-up period. Two patients suffered high-energy (fall 3 m down a staircase and bicycle accident) fractures; several ribs, a clavicle, and a

Table 1 Baseline characteristics

	All women ($n = 67$)	ODN-ODN ($n = 39$)	PCB-ODN ($n = 28$)
Age	78 (77–79)	78 (77–79)	78 (76–80)
Weight (kg)	60 (58–63)	61(58–65)	59 (55–64)
Height (m)	160 (158–161)	159 (157–161)	160 (158–162)
BMI (kg/m^2)	24 (23–25)	24 (23–26)	23 (21–25)
LSBMD (g/cm^2)	0.932 (0.892–0.971)	0.954 (0.898–1.01)	0.898 (0.842–0.954)
THBMD (g/cm^2)	0.708 (0.688–0.728)	0.716 (0.689–0.743)	0.700 (0.669–0.731)
FNBMD (g/cm^2)	0.592 (0.574–0.609)	0.599 (0.573–0.625)	0.581 (0.558–0.603)

Results are presented with mean values and 95% CI. *BMI*, body mass index; *BMD*, bone mineral density; *LSBMD*, BMD lumbar spine; *THBMD*, BMD total hip; *FNBMD*, BMD femoral neck

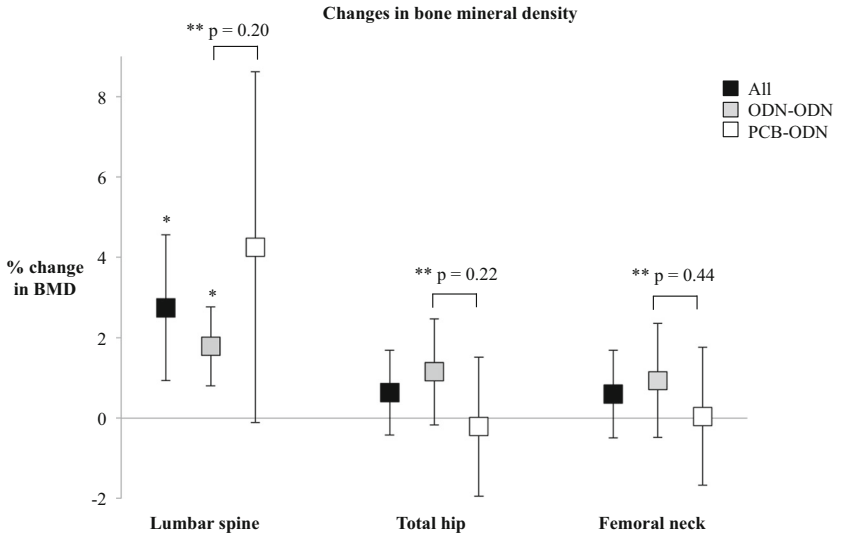

Fig. 1 Changes in bone mineral density at the lumbar spine, total hip, and femoral neck. All: all participants. ODN-ODN group, patients treated with ODN for 7 years. PCB-ODN group: patients treated with ODN for 2 years and placebo for 5 years. *Significant change from baseline to month 12 within groups (paired-samples *t* test). **Change from baseline to month 12 between groups (independent *t* test)

pertrochanteric hip fracture. One patient suffered a low-energy wrist fracture.

Discussion

Treatment with ZOL 5 mg subsequent to treatment with ODN 50 mg weekly for approximately 7 or 2 years increased LSBMD and maintained THBMD and FNBMD. The BTMs were suppressed and in the lower end of the premenopausal reference interval 3 months after treatment with ZOL. As expected, the BTM increased during the following months [23–25]. However, 12 months after the ZOL infusion, the BTMs were in the middle of the premenopausal reference range indicating continued suppression of bone turnover.

Calcium metabolic markers also changed during the 12 months following the ZOL infusion. During the LOFT trial and at baseline in the present follow-up study, patients were advised to secure a daily intake of 1000 mg calcium and 20–40 μg vitamin D. Unfortunately, in the majority of the participants, the intake of vitamin D and calcium was not in accordance with this. Thus, the changes seen in the calcium metabolic markers could be explained by the fact that supplementation was not optimized until month 3 when the first measurements of vitamin D and PTH during the follow-up study were performed. The increased intake of calcium and vitamin D would lead to an increase in plasma/serum vitamin D and a corresponding decrease in plasma PTH between months 3 and 12. Additionally, it has previously been demonstrated that ZOL treatment may cause a secondary increase in p-PTH, which also could contribute to the changes in p-PTH [26].

The phase II clinical trial of ODN demonstrated that BMD decreased at all sites in 92 postmenopausal women with osteoporosis discontinuing ODN 50 mg weekly after 2 years [17]. Within 3 months of discontinuing ODN, CTX had increased to 120% above baseline and hereafter slowly decreased

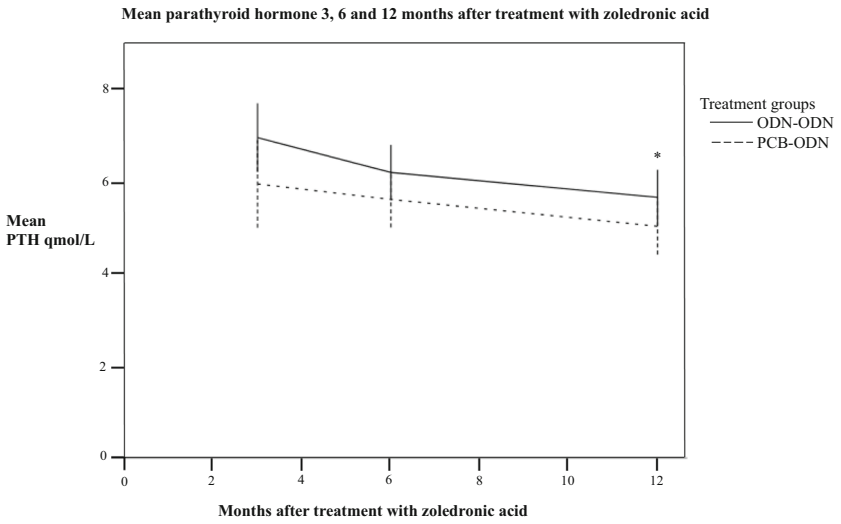

Fig. 2 Mean parathyroid hormone (PTH) 3, 6, and 12 months after treatment with zoledronic acid. Mean values with 95% confidence intervals. PTH was significantly lower in the PCB-ODN group compared to the ODN-ODN group ($p = 0.016$). Significant difference ($p = 0.007$)

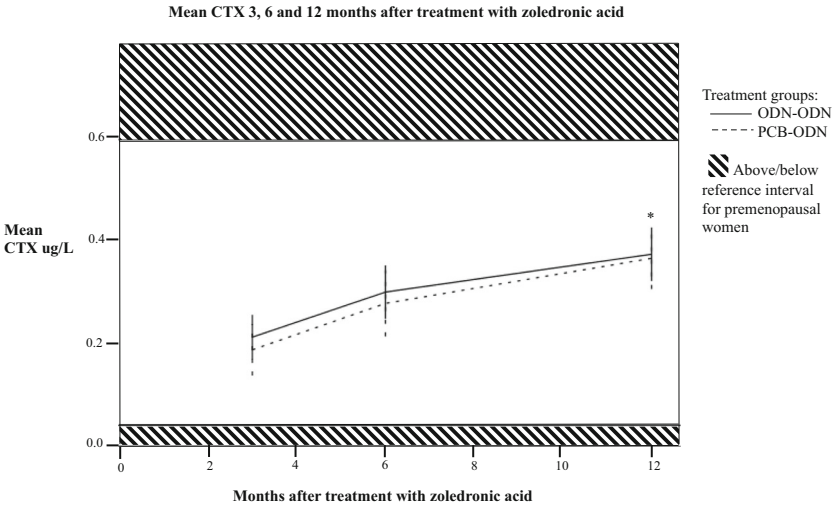

Fig. 3 Mean C-terminal collagen crosslinks (CTX) 3, 6, and 12 months after treatment with zoledronic acid. There are only 57 measurements of CTX at month 3. Mean values with 95% confidence intervals. *Significant difference ($p < 0.001$)

towards baseline at the end of the third year in the clinical trial. Similarly, 6 months after stopping ODN, the formation markers BSAP and PINP had increased to 34% and 90%, respectively, above baseline, however, these markers also returned to baseline at the end of the third year [17]. There was a greater bone loss on the first 6 months after stopping ODN treatment as compared to the following 6 months, and after 3 years, LSBMD and THBMD had returned to baseline values. Similar BMD changes have also been reported by others [16]. The effects of discontinuing ODN have also been evaluated in ovariectomized rabbits [27]. Duong and colleagues examined changes in BTM, bone strength, and BMD in 7.5-month-old ovariectomized rabbits discontinuing ODN after treatment for 8 months [27]. The animals were examined 4 and 8 months after discontinuing ODN. As expected, aBMD and vBMD declined to values similar to placebo-treated rabbits. Additionally, bone strength of the lumbar spine and central femur in the ODN-placebo treated animals were similar to the values in the placebo-treated rabbits. The bone resorption marker, urinary alpha helical peptide (uHP) fragments of type I collagen, increased significantly to 65% above the levels in placebo-treated animals [27]. Unlike the findings from the clinical trial [17], BSAP did not change significantly in the rabbits discontinuing ODN. The authors speculate whether the difference might be explained by differences in species [27].

As illustrated by the rapid BMD loss, BTM increases, and decreased bone strength on the first months after discontinuing ODN [17], treatment with ODN is considered to be reversible and stopping treatment is characterized by increased bone turnover. A case report has described multiple vertebral fractures after discontinuation of ODN with the first fractures occurring only 4 months after stopping treatment [21]. It has been speculated that the elevated fracture risk in patients previously treated with ODN is due to increased bone remodeling causing microarchitectural deterioration [21]. The present follow-up study was not powered to evaluate if treatment with ZOL after ODN prevent fractures; however, the

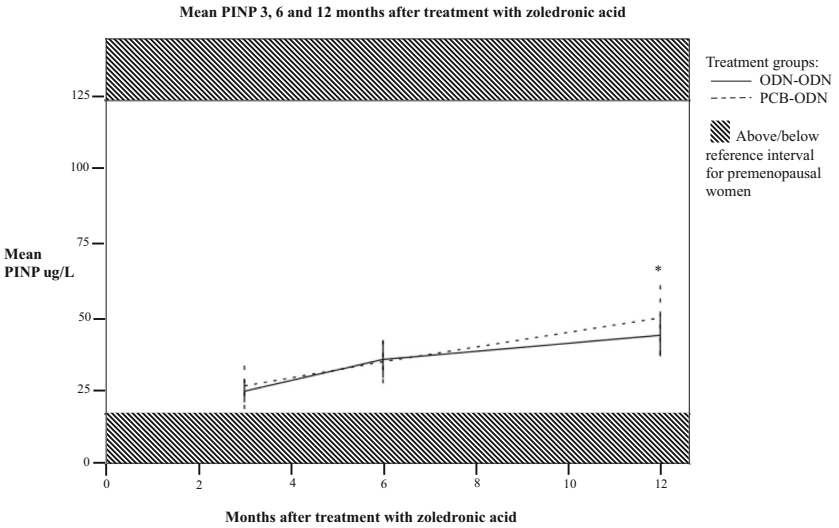

Fig. 4 Mean procollagen type I N-terminal propeptide (PINP) 3, 6, and 12 months after treatment with zoledronic acid. There are only 57 measurements of PINP at month 3. Mean values with 95% confidence intervals. *Significant difference ($p < 0.001$)

Table 2 Bone turnover markers and calcium metabolic parameters

	Reference interval	3 months ($n = 59$)	6 months ($n = 59$)	12 months ($n = 59$)	p value[1]
s-PINP	17–124 μg/L[2]	25 (22–29)	35 (31–40)	46 (40–52)	$p < 0.001$*
s-CTX	0.04–0.59 μg/L[2]	0.20 (0.17–0.23)	0.29 (0.25–0.33)	0.37 (0.33–0.40)	$p < 0.001$*
p-Osteocalcin	13–55 μg/L	17 (16–19)	19 (17–20)	22 (20–24)	$p = 0.001$*
s-Bone-specific alkaline phosphatase	5.5–27.1 μg/L	13 (12–14)	15 (14–16)	16 (15–18)	$p = 0.001$*
s-25-Hydroxyvmitamin (D2 + D3)	50–160 nmol/L	100 (93–107)	110 (102–119)	110 (103–119)	$p = 0.059$
p-Ionized calcium	1.18–1.32 mmol/L	1.24 (1.23–1.25)	1.25 (1.24–1.26)	1.24 (1.23–1.26)	$p = 0.20$
p-eGFR	> 60 ml/min	71 (67–75)	70 (66–74)	69 (65–73)	$p = 0.014$*
p-Parathyroid hormone	1.6–6.9 pmol/L	6.6 (6.0–7.2)	6.0 (5.6–6.4)	5.4 (5.0–5.9)	$p = 0.007$*

Laboratory measurements 3, 6, and 12 months after treatment with ZOL. Results are presented with mean values and 95% CI. *eGFR*, estimated glomerular filtration rate; *CTX*, C-terminal collagen crosslinks; *PINP*, procollagen type I N-terminal propeptide. There are only 57 measurements of osteocalcin at month three

[1] Repeated measures

[2] Reference interval for premenopausal women

*Significant change over time

study did show continuously suppressed bone turnover markers 12 months after treatment with ZOL as well as increased LSBMD which may suggest a low risk of fracture.

Discontinuation of DMAB has been associated with vertebral and multiple vertebral fractures [12, 18–20, 28–31]. The suppression of bone turnover seen with ODN is not as marked as that seen with DMAB [16, 17, 32], and the mechanisms by which the two drugs suppress osteoclast activity are different. DMAB predominantly prevents recruitment of OCs whereas ODN prevents resorptive activity of the OCs. Zhuo et al. investigated the effect of ODN on the OCs using a synchronized culture of human OCs [22]. During treatment with ODN, the number and size of the OC were increased; however, upon discontinuing treatment, the size decreased to that of the vehicle-treated OC and furthermore, the number of OC was somewhat reduced, but still remained above that of the vehicle-treated OC. Due to these differences, the reversibility and the rebound activation of bone resorption may be less after discontinuation of ODN. Three case series report the effect of treatment with ZOL subsequent to DMAB [13–15]. Horne et al. found a 73–87% preservation of the gain in BMD in patients previously treated with ZOL after romosozumab for 1 year followed by DMAB for 2 years [15]. Lehmann et al. presented a case series comprising 22 postmenopausal women treated with a single infusion of ZOL after 2 years of treatment with DMAB [13]. Approximately 33% of the bone mass at the lumbar spine gained during treatment with DMAB was lost. Lastly, Reid et al. demonstrated a significant decline in BMD at the lumbar spine ($p = 0.043$) and hip ($p = 0.005$) in six postmenopausal women treated with a single infusion of ZOL after treatment with DMAB for 7 years [14]. In none of the studies, treatment with ZOL subsequent to treatment with DMAB was able to fully preserve BMD. The present study demonstrated that a single infusion of ZOL after discontinuation of ODN is sufficient to continuously suppress bone turnover and maintain BMD for up to 1 year. This suggests that ODN suppresses bone turnover to a lesser degree than DMAB and although the effect of ODN is reversible, the reversibility can be controlled by a single infusion of ZOL.

Our follow-up study has strengths and several limitations. The strengths are the homogenous study population consisting of two well-defined groups of women who had been treated for 2 or 7 years with ODN in the setting of a phase III clinical trial prior to inclusion in this study and that 84% of the women participating in LOFT extension at our site participated in this follow-up study. The most important limitation is the lack of a placebo group. When the study was designed, it was known that discontinuing ODN would lead to reactivation of bone resorption [16, 17], and numerous case reports have reported multiple vertebral fractures in women discontinuing DMAB [18–20, 28–31]. We therefore found it unethical to include a placebo group. Thus, we therefore do not know how the BTM and BMD would have changed in our study population had they not been treated. The increase in the LSBMD seen in the treated women could partly be explained by a progression of degenerative conditions, osteoarthritis, or calcification of aorta [33]; however, in the study of Eisman et al., bone mass decreased after discontinuation of ODN after 2 years which is similar to the treatment duration in women in the PCB-ODN group. Since BMD changes after ZOL infusion were similar between women treated with ODN for 2 or 7 years before discontinuation, we find it unlikely that the changes seen in LSBMD are fully explained by progression of degenerative changes. Another limitation is the absence of biochemical measurements at baseline. In the HORIZIN trial, the mean CTX increased approximately 100% (0.1 to 0.2 ng/ml) from

month 6 to month 12 after ZOL treatment [25]. The mean increase in CTX in our follow-up study from month 3 to month 12 was approximately 85% and 28% from month 6 to month 12. Thus, the increase in p-CTX from the lowest measured value after ZOL is comparable to the results from the HORIZON trial.

Supplementation with calcium and vitamin D could not optimized until biochemical results were obtained after 3 months; however, the modest changes in serum levels of vitamin D and PTH did not affect changes in bone turnover markers or BMD (data not shown). Finally, this is a small follow-up study with a limited number of participants, which would not allow investigating the effects of ODN discontinuation on fracture risk.

Conclusion

A single infusion of ZOL 5 mg subsequent to treatment with ODN 50 mg weekly for approximately 7 or 2 years increased lumbar spine BMD and maintained BMD at the total hip and femoral neck 12 months after the treatment. The BTMs remained suppressed or in the lower part of the premenopausal reference interval indicating low bone turnover.

Compliance with ethical standards

Conflict of interest Torben Harsløf received lecture fees from Amgen, Astra Zeneca, and Eli Lilly. Bente Langdahl is a consultant for MSD, Amgen, Eli Lilly, and UCB and has received lecture fees from MSD, Eli Lilly, and Amgen. Anne Sophie Koldkjær Sølling has nothing to declare.

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