Parathyroid hormone changes following denosumab treatment in postmenopausal osteoporosis

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Introduction: Denosumab is a fully human monoclonal antibody to RANKL and represents a distinct class of antiresorptives in osteoporosis treatment, since it inhibits osteoclast maturation in the early stages of development and osteoclast activity, rather than impairing viability of osteoclasts. In both preclinical and clinical studies denosumab induced a dose-dependent increase in parathyroid hormone (PTH) levels. This increase in PTH is considered compensatory against the transient dose-dependent decrease in serum calcium levels, while hypocalcemic events seem infrequent even among subjects not receiving calcium and/or vitamin D (Ca/D) supplements.

In this study we monitored PTH changes following a single injection of denosumab. The primary end point was the alteration of PTH 1 month after the injection while receiving a commonly used (1 gr/800 IU) or double-dose (2 gr/1,600 IU) supplementation with calcium and vitamin D. The secondary end point was the alteration of PTH 6 months after denosumab injection.

Methods:
Design: Prospective, multicenter, study among postmenopausal women followed for 6 months.
Patients: 47 postmenopausal women followed in 2 outpatient clinics, requiring onset or continuation of osteoporosis treatment. We administered 1 gr calcium carbonate and 800 IU cholecalciferol daily for 6 months (Group A) or the double dose for the first month followed by the 1 gr/800 IU Ca/D regimen for the next 5 months (Group B) (Figure 1).
Measurements: PTH alterations between and within groups, and their associations with serum Ca and bone markers.

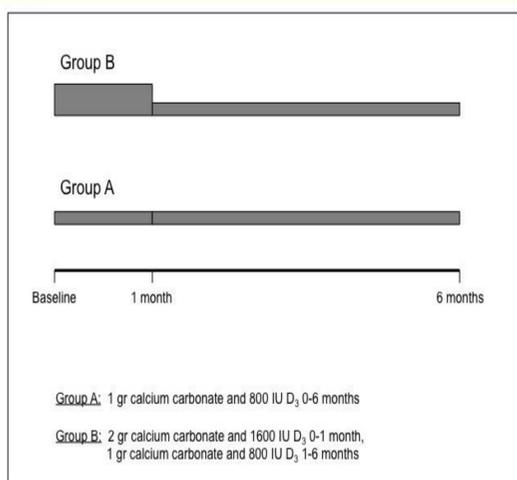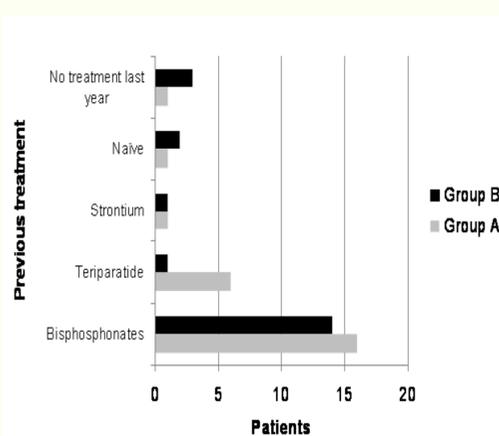Figure 1: Calcium and cholecalciferol administration

Group A: 1 gr calcium carbonate and 800 IU D₃ 0-6 months

Group B: 2 gr calcium carbonate and 1600 IU D₃ 0-1 month,
1 gr calcium carbonate and 800 IU D₃ 1-6 months

Figure 2: Previous treatment

Table 1. Clinical, demographic and Bone Mineral Density data of both groups at baseline

Variable	Group A	Group B	P-value
Age (years)	67·9 ± 1·9	67·3 ± 2·4	0·843
BMI (kg/m²)	26·2 ± 0·9	29·4 ± 1·1	0·067
BMD Lumbar spine (g/cm²)	0·828 ± 0·018	0·873 ± 0·015	0·066
BMD femoral neck (g/cm²)	0·689 ± 0·020	0·688 ± 0·017	0·97
BMD Lumbar spine (T-score)	−2·8 ± 0·1	−2·3 ± 0·11	0·009
BMD femoral neck (T-score)	−2·4 ± 0·2	−2·6 ± 0·1	0·514

BMI, Body Mass Index; BMD, Bone Mineral Density.

Results: There were no between group differences regarding previous treatment (p=0.325) (Figure 2) or regarding previous bisphosphonate use (p=0.820). Eight patients had previously experienced one, two patients had two, and one patient had three low-energy fractures (p=0.258 for between group fractures at baseline). No significant differences were found at baseline regarding BMD and biochemistry (Tables 1 and 2).

Regarding between group differences (Group A vs. Group B), month 1 and month 6 comparative data were similar, except for P1NP, which was significantly higher in Group A than B at month 1 (Table 2). However, the mean percent change between month 1 and baseline for PTH [Δ(PTH$_{1-0}$)] was significantly higher in Group A than B (63.5% ± 28.2% vs. -3.0% ± 4.7%, p=0.029), whereas Δ(Corrected calcium$_{1-0}$) was significantly lower in Group A than B (-2.8% ± 1.3% vs. 0.4% ± 0.5%, p=0.031); there were no significant changes in Δ(P1NP$_{1-0}$) and Δ(CTX$_{1-0}$) (Figure 3).

Regarding within group differences, PTH levels were significantly higher at month 1 and 6 in A, but not in Group B (Table 1). Corrected calcium levels were significantly decreased in Group A, but not in Group B, at month 1 and returned to baseline values at month 6 (Table 2). Phosphate levels were not significantly changed in either group.

Δ(PTH$_{1-0}$) was significantly inversely correlated with Δ(corrected calcium$_{1-0}$) (r$_s$= -0.610; p=0.002), and Δ(CTX$_{1-0}$) (r$_s$= -0.697; p=0.003) in Group A, but not in Group B (r$_s$= -0.181; p=0.433, r$_s$= -0.052; p=0.823, r$_s$= -0.30; p=0.893, respectively).

No adverse event, including hypo- or hypercalcaemia and hypercalciuria, was recorded throughout the study.

Conclusion: Calcium and vit. D supplementation at a dose of 2gr/1,600 IU, but not 1gr/800 IU, attenuated the decrease in serum Ca and the compensatory increase in PTH following a single s.c. injection of denosumab 60mg. Therefore, an increase of PTH should be expected, at least following the first administration of denosumab in common clinical practice. The effect of this compensatory consequence in bone metabolism warrants further investigation.

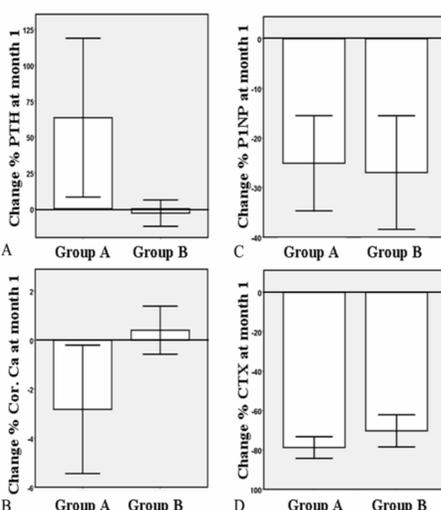Figure 3: Alterations of PTH, Ca, P1NP and CTX levels at month 1.

Table 2. Baseline, 1 month and 6 month comparative data of both groups

Variable	Group	Baseline	Month 1	P-value between baseline and month 1	Month 6	P-value between month 1 and 6	P-value between baseline and month 6
PTH (pg/mL)	A	34·8 ± 2·8	62·4 ± 13·3	0·026	40·7 ± 4·0	0·532	0·029
	B	41·7 ± 2·6	39·8 ± 2·8	0·263	44·2 ± 4·2	0·638	0·567
P-value between groups		0·079	0·982		0·553		
25(OH) vitamin D (ng/mL)	A	26·9 ± 2·6	28·4 ± 2·7	0·590	36·6 ± 4·1	0·009	0·016
	B	27·2 ± 2·0	28·4 ± 1·7	0·464	35·7 ± 2·6	0·004	0·002
P-value between groups		0·993	0·989		0·848		
P1NP (ng/mL)	A	49·1 ± 8·2	33·6 ± 4·1	0·001	16·6 ± 2·0	0·005	0·001
	B	37·4 ± 6·0	26·4 ± 5·8	0·001	17·8 ± 3·1	0·004	<0·001
P-value between groups		0·144	0·020		0·875		
CTX (ng/mL)	A	0·226 ± 0·045	0·035 ± 0·003	<0·001	0·105 ± 0·015	<0·001	0·005
	B	0·223 ± 0·040	0·054 ± 0·010	<0·001	0·112 ± 0·015	<0·001	0·001
P-value between groups		0·894	0·240		0·773		
Corrected calcium (mg/dL)	A	9·5 ± 0·1	9·3 ± 0·1	0·031	9·6 ± 0·1	0·003	0·758
	B	9·3 ± 0·1	9·4 ± 0·1	0·469	9·4 ± 0·1	0·383	0·127
P-value between groups		0·068	0·524		0·329		
Phosphate (mg/dL)	A	3·7 ± 0·1	3·5 ± 0·1	0·136	3·6 ± 0·1	0·882	0·131
	B	3·8 ± 0·1	3·8 ± 0·1	0·894	3·7 ± 0·1	0·392	0·496
P-value between groups		0·524	0·061		0·554		
eGFR (mL/min/1·73 m²)	A	73·6 ± 3·0	70·4 ± 3·4	0·163	69·3 ± 3·4	0·362	0·117
	B	73·7 ± 4·3	73·6 ± 4·6	0·883	73·0 ± 4·6	0·700	0·731
P-value between groups		0·953	0·582		0·527		

Data are presented as mean ± standard error of the mean (SEM); CTX, C-terminal telopeptide; PINP, procollagen type I N-terminal propeptide; PTH, parathyroid hormone.