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 antiresorptive agents 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 (CaD) supplements.

In this study we monitored PTH changes following a single injection of denosumab. The primary endpoint was the alteration of PTH 1 month after the injection while receiving a commonly used (1 gr/800 IU) or double-dose (2 gr/1600 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 CaD 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.

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, PTH levels were significantly higher at month 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 2 (Table 2). Phosphate levels were not significantly changed in either group. ΔPTH1 was significantly inversely correlated with Δcorrected calcium1 (r=-0.610; p=0.002), and ΔCTX1 (r=-0.697; p=0.003) in Group A, but not in Group B (r=-0.181; p=0.433, r=-0.052; p=0.823, r=-0.30; p=0.893, respectively).

No adverse event, including hypo- or hypercalcemia, was recorded throughout the study.

Conclusion: Calcium and vit. D supplementation at a dose of 2gr/1600 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.