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Denosumab in treatment-naïve and pre-treated with zoledronic acid postmenopausal women with low bone mass: Effect on bone mineral density and bone turnover markers

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ABSTRACT

Purpose. To compare denosumab-induced changes in lumbar spine (LS) and femoral neck (FN) bone mineral density (BMD), bone markers and free soluble receptor activator of nuclear factor kappaB ligand (sRANKL) between treatment naïve postmenopausal women with low bone mass (naïve group) and those who were previously treated with a single zoledronic acid infusion (post-Zol group).

Procedures. Procollagen type 1 N-terminal propeptide (P1NP), C-terminal cross-linking telopeptide of type 1 collagen (CTx) and sRANKL levels were measured in serum samples obtained at baseline and 3, 6 and 12 months after denosumab initiation. LS and FN BMD were measured at baseline and 12 months.

Results. LS and FN BMD increased significantly in both naïve and post-Zol group ($p < 0.001$ and $p = 0.025$ vs. $p < 0.001$ and $p = 0.017$, respectively). Despite the higher P1NP and CTx levels in naïve patients at baseline (both $p < 0.001$), denosumab caused comparable decreases in both groups at month 3, which returned to post-Zol group baseline levels at

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density; BMI, body mass index; CCa, corrected calcium; CTx, C-terminal telopeptide of type 1 collagen; FN, femoral neck; LS, lumbar spine; PTH, intact parathyroid hormone; P1NP, procollagen type 1 N-terminal propeptide; RANKL, receptor activator of nuclear factor κ-B ligand; sRANKL, soluble receptor activator of nuclear factor κ-B ligand; tALP, total alkaline phosphatase.

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month 6 and 12 in all patients. Similarly, sRANKL levels decreased significantly at month 3 in both groups and returned to baseline levels at months 6 and 12.

Conclusions. In patients previously treated with zoledronic acid, sequential denosumab treatment is effective in terms of BMD increases and bone turnover suppression. Despite the lower baseline levels in patients pre-treated with zoledronic acid, bone markers are similarly decreased in both groups following denosumab administration and maintain their reversibility. Denosumab reversibly suppresses endogenous free sRANKL levels in both naïve and zoledronic acid pre-treated patients.

1. Introduction

Denosumab, a monoclonal antibody against the receptor activator of nuclear factor κ-B ligand (RANKL), is a potent antiresorptive agent [1], with a mechanism of action that differs from bisphosphonates, resulting in discrete effects on bone metabolism [2] and bone mass [3]. Denosumab is characterized by a year-by-year continuous increase of bone mineral density (BMD) for as long as it is administered [3] and a rapid reversibility of its effect on bone turnover and BMD upon discontinuation [4]. On the other hand, zoledronic acid is considered the most potent bisphosphonate [5] and its effects on the skeleton remain for years after discontinuation [6].

Previous treatment with bisphosphonates blunts the skeletal effect of any sequential treatment with other agents including denosumab [7–9]. Indeed, increases of BMD with denosumab were more pronounced in treatment naïve patients [10] compared to patients previously treated with alendronate [7] or other oral bisphosphonates [8,9]. However, since zoledronic acid is a potent bisphosphonate and has a different route and frequency of administration, sequential treatment with denosumab might not have the skeletal effects reported in the above studies.

The primary end point of this study was the effect of one year of treatment with denosumab on lumbar spine (LS) BMD of postmenopausal women with low bone mass either previously treated with zoledronic acid for one year or treatment-naïve. Secondary end points included the effect on femoral neck (FN) BMD, bone turnover markers (procollagen type 1 N-terminal propeptide [P1NP] and C-terminal telopeptide of type 1 collagen [CTx]), and serum free soluble RANKL (sRANKL) levels.

2. Patients and Methods

2.1. Patients

This was an interventional, prospective, open label clinical trial. Patients were recruited at the outpatient clinics for Metabolic Bone Diseases of 424 General Military Hospital, Thessaloniki, Greece. Postmenopausal Caucasian women with low bone mass (BMD T-score of less than or equal to −2.0 at the LS and/or the non-dominant FN) were assigned to naïve group, if they had not previously received any anti-osteoporotic treatment, or post-Zol group if they had received a single dose of zoledronic acid one year ago. The patients of both groups received one-year treatment with denosumab, 60 mg s.c. every six months (2 doses in total). Exclusion criteria for both groups were: i) age <40 years; ii) any bone and mineral disorder other than osteoporosis, including primary or secondary hyperparathyroidism, Paget's disease of bone, osteogenesis imperfecta, rheumatologic diseases, paraplegia, chronic immobilization; iii) severe liver or kidney disease (creatinine clearance <60 ml/min/1.73 m^2) or liver or kidney transplantation; iv) premature ovarian failure; v) uncontrolled thyroid disease; vi) any malignancy; vii) any musculoskeletal injury or surgical procedure 6 months prior to baseline; viii) history or concomitant medications that could affect bone metabolism, including immunosuppressive, anticonvulsant, antiviral and anti-tuberculosis agents, addictive drugs, corticosteroids, non-steroidal anti-inflammatory drugs, amiodarone, thiazolidinediones, interferon, metronidazole and tamoxifen. All patients received supplements of calcium 1000 mg/d and vitamin D 800 IU/d throughout the study. The study was approved by the local ethics committee and was in accordance with the Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice. All patients provided informed consent before entering the study.

2.2. Methods

At baseline, all patients provided a detailed history and were subjected to physical examination, body mass index (BMI) calculation, and areal BMD measurement by dual energy X-ray absorptiometry (DXA) at LS and FN, using a DPX-IQ densitometer (Lunar Corporation, Madison, WI). BMD measurements were repeated twelve months (±2 weeks) after denosumab initiation. After an overnight fast, morning (08:00–09:00 pm) blood samples were obtained from all patients at baseline and three, six and twelve months following denosumab initiation. Serum total calcium, phosphate, total serum alkaline phosphatase (tALP) and albumin for total calcium correction were measured within 1 h after blood collection. Additional samples were centrifuged and serum was separated and stored at −70 °C; all the remaining studied parameters were measured in one batch at the end of the study. These included P1NP (ECLIA, Elecsys total P1NP, Roche Diagnostics, Mannheim, Germany; intra- assay coefficient of variation [CV] 1.3–3.0%, inter-assay CV 2.2–4.1%), CTx (ECLIA, Elecsys Crosslaps, Roche Diagnostics, Mannheim, Germany; intra-assay CV 2.0–3.5%, inter-assay CV 2.8–8.4%), sRANKL (free soluble RANKL High Sensitivity ELISA [3rd generation], Biomedica Medizinprodukte, Wien, Austria; intra-assay CV ≤5%, inter-assay CV ≤3%, detection limit 0.01 pml/L), intact parathyroid hormone (PTH; ECLIA,