The Transitory Increase in PTH Following Denosumab Administration is Associated With Reduced Intracortical Porosity: a Distinctive Attribute of Denosumab Therapy.

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The benefit of an antiresorptive upon the material composition and structure of bone is largely determined by its direct and indirect effects on the volumes of bone resorbed and deposited by each bone remodeling unit (BMU), and by the number of BMUs inhibited in both the trabecular and cortical compartments. Denosumab (DMAb) rapidly reduces bone resorption by existing BMUs and markedly inhibits the birth rate of new BMUs during the initial months following administration. This acute remodeling reduction is accompanied by a transitory increase in circulating PTH which could increase osteoblast longevity and/or activity. We hypothesized that the direct effect of DMAb on resorption inhibition, and the possible indirect effect on bone formation mediated by an increase in PTH in the face of inhibited osteoclastic activity by the BMU, would reduce cortical porosity in women at risk for fracture.

Postmenopausal women (N=247) with a mean (SD) age of 60.6 (5.4) yrs and low BMD were randomly assigned in a double-blind, double-dummy trial to DMAb 60mg Q6M (N=83), alendronate (ALN) 70mg QW (N=82), or placebo (Pbo; N=82). PTH was measured at baseline (BL), wk 1, and mos 1, 3, 6, 6.25, 7, 9, and 12. An area under the curve (AUC) for PTH was derived from the change from BL for each subject. Porosity was evaluated in the compact-appearing cortex of the distal radius at BL and mo 12 by HR-pQCT. Associations between PTH AUC and change in porosity were evaluated.

Transitory increases in PTH were seen in the DMAb and ALN groups, but not in the Pbo group (Fig 1). The increase in PTH was larger following DMAb than ALN (P<0.05) and was observed after each DMAb dose. At the radius by 12 mos, porosity increased in the Pbo group, increased less in the ALN group, and was reduced by DMAb (+5.2%, +2.9%, and -3.0%, respectively). In the Pbo and ALN groups, porosity increased with increasing PTH (Fig 2). With DMAb, porosity decreased as PTH increased. These relationships were maintained after adjusting for BL remodeling.

In conclusion, DMAb partly reverses microarchitectural deterioration; predominately by directly reducing bone remodeling intensity, but perhaps also indirectly, by transiently increasing PTH, and so positively influencing BMU balance. The results describe a unique mechanism of DMAb action due to its direct effect to fully and transiently increasing PTH, and so positively influencing BMU balance. The results describe a unique mechanism of DMAb action due to its direct effect to fully and transiently increasing PTH, and so positively influencing BMU balance.

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Purpose: Denosumab (DMAb) is an approved therapy for the treatment of postmenopausal women with osteoporosis at increased risk for fracture. A favorable DMAb risk/benefit profile was demonstrated in the pivotal, 3-year FREEDOM trial. All women who completed FREEDOM were eligible to participate in an extension to investigate the safety and efficacy of DMAb treatment for up to 10 years. We previously reported that 5 years of DMAb treatment maintained bone turnover reduction, increased BMD, and was associated with low fracture rates. Here, we provide details on the yearly incidence of serious adverse events (SAEs) of infection and adverse events (AEs) of malignancy in FREEDOM and the extension.

Methods: Of the 6478 women who completed FREEDOM, 4550 (70%) enrolled in the extension, during which, all women receive 60 mg DMAb every 6 months and supplemental calcium and vitamin D daily. For the analyses reported here, women from the FREEDOM DMAb group received 2 more years of DMAb for a total of 5 years of exposure (long-term group; N=2343) and women from the FREEDOM placebo group received 2 years of DMAb exposure (cross-over group; N=2207). The analyses of AEs were descriptive and are reported as exposure-adjusted subject incidence rates.

Results: The year-to-year observed subject incidence rates of SAEs of infection (Table 1) and AEs of malignancy (Table 2) in the placebo group exhibited some variation during the 3 years of the FREEDOM trial. The yearly subject incidence rates in the first 2 years of the extension for the long-term and cross-over groups were similar to or lower than the observed yearly rates in the FREEDOM placebo group. This was also the case for individual SAEs of infection (by preferred term) including cellulitis or erysipelas (Table 1) and individual malignancies (by preferred term; Table 2).

One case of oral osteomyelitis and one case of bone necrosis in the cross-over group were adjudicated as consistent with ONJ.

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Conclusions: The year-to-year observed AE rates in placebo subjects provide a valuable indicator of the expected variation in untreated subjects and assist in the interpretation of safety results associated with therapy. Yearly incidences of SAEs of infection and AEs of malignancies did not increase over 5 years of continuous DMAb treatment of postmenopausal women with osteoporosis. The imbalances in SAEs of skin infections reported in the original FREEDOM study were not observed with DMAb treatment in the extension study.

Table 1

Table 2

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Reduction in Incidence of Vertebral Fractures with Once Yearly Zoledronic Acid in Men with Osteoporosis. Steven Boonen1, Jean-Marc Kaufman2, Jean-Yves Reginster3, Rene Rizzoli4, Kurt Lippuner5, Dirk Vanderschueren6, Josef Hruska1, Oscar Antunez7, Philemon Papathanasiou8, Guoqin Su8, Eric Orwoll9. 1Katholieke Universiteit Leuven, Belgium, 2University Hospital of Ghent, Belgium, 3University of Liege, Belgium, 4University Hospitals & Faculty of Medicine of Geneva, Switzerland, 5Osteoporosis Policlinic, University of Bern, Switzerland, 6Leuven University Hospital, Belgium, 7Novartis Pharma AG, Switzerland, 8Novartis Pharmaceuticals, USA, 9Oregon Health & Science University, USA

Introduction
Male osteoporosis and associated fracture risk have not been adequately studied and, to date, therapeutic trials in osteoporotic men have not included fracture endpoints. This 24-month multicentre, randomized, controlled trial investigated the efficacy and safety of annual intravenous zoledronic acid 5 mg (ZOL) in men with osteoporosis.

Methods
In total, 1199 men (range 50-85 years) with primary osteoporosis, or secondary osteoporosis due to hypogonadism, were randomized to receive once-yearly ZOL as a 15-min intravenous infusion or placebo (PBO). Patients also received daily calcium 1000-1500 mg and vitamin D 800-1200 IU. The primary endpoint was the proportion of patients with >1 new morphometric vertebral fracture over 24 months. Secondary endpoints included changes in biochemical markers of bone resorption and formation including \( \beta \)-CTX and PINP, change in height, and overall safety.

Results
At baseline, 32.1% of patients had >1 vertebral fractures. The proportion of patients with >1 new morphometric vertebral fracture over 24 months was significantly lower in the ZOL group (1.6%), compared with the PBO group (4.9%; odds ratio 0.32; 95% CI 0.14, 0.66 [relative risk reduction 67%; 95% CI 30–84, \( p=0.0016 \)) [Graph]. ZOL also reduced moderate–severe fractures by 63% compared with placebo. Over 24 months, ZOL showed significantly lower serum \( \beta \)-CTX and PINP levels relative to PBO (\( p<0.0001 \)) at all post-baseline timepoints. With these markers, a significant between-treatment difference was achieved at Month 3 and maintained over the 24-month period. Men treated with ZOL for 24 months experienced less height loss than those treated with PBO (LSM –2.34 mm vs –4.49 mm, respectively; \( p=0.0020 \)). ZOL was generally well-tolerated, with a similar incidence of serious adverse events between groups (ZOL, 25.2%; PBO, 25.3%).

Conclusion
Treatment with ZOL for a period of 24 months reduces the risk of new vertebral fractures in men with osteoporosis. This is the first clear demonstration of the efficacy and safety of bisphosphonate treatment for fracture risk reduction in men with osteoporosis.

Table 1: Yearly Incidence of Serious Adverse Events of Infections

Table 2: Yearly Incidence of Serious Adverse Events of Malignancies

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