DENOSUMAB RESTORES CORTICAL BONE LOSS AT THE 1/3 RADIUS ASSOCIATED WITH AGING AND REDUCES WRIST FRACTURE RISK

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The skeleton is 80% cortical bone, and cortical bone loss contributes importantly to increased fracture risk. Denosumab (DMAb) has been shown to increase BMD at sites of cortical bone, including the 1/3 radius, a skeletal site not responsive to most osteoporosis

treatments. DXA measurements over time allow for tracking changes in BMD, a known predictor of fracture risk. Here, we examined changes over time in 1/3 radius BMD and wrist fracture incidence during 3 yrs of placebo (Pbo) in the FREEDOM trial and 6 subsequent yrs of DMAb therapy in the FREEDOM Extension (EXT).

We evaluated wrist fractures in 2207 women who enrolled in the EXT and had received Pbo during FREEDOM (3 yrs), and DMAb 60 mg Q6M during EXT (6 yrs) (cross-over group); all women received daily calcium and vitamin D. A subset of these women (n = 115) participated in a 1/3 radius DXA substudy and were evaluated at baseline, FREEDOM (yrs 1–3), and EXT (yrs 1–3 and 5). Analysis of mean percentage changes in BMD over time from FREEDOM and EXT baselines consisted of a repeated measures model. Wrist fracture rates (per 100 subject-yrs), rate ratios, and 95% confidence intervals (CI) were computed through EXT Yr 6.

At FREEDOM baseline, the mean (SD) 1/3 radius T-score was −2.53 (1.18). During FREEDOM, daily calcium and vitamin D alone resulted in a progressive and significant loss of BMD at the 1/3 radius over 3 yrs (−1.2%; $p < 0.05$ compared with FREEDOM baseline); on DMAb initiation during the EXT, this bone loss was reversed, resulting in BMD gains at the 1/3 radius of 1.5% at EXT Yr 5 ($p < 0.05$ compared with EXT baseline). During the FREEDOM Pbo period, the wrist fracture rate was 1.02 (95% CI = 0.80–1.29) per 100 subject-yrs. In the first 3 yrs of the EXT, during which time the BMD lost with Pbo recovered in response to DMAb and returned to original baseline levels, the subjects' wrist fracture rate remained comparable to that observed during their FREEDOM Pbo period. With DMAb administration over the subsequent 2 yrs resulting in BMD increases above the original FREEDOM baseline, the number of wrist fractures was markedly reduced and the wrist fracture rate declined to levels significantly lower than the FREEDOM Pbo rate (rate ratio = 0.57, 95% CI = 0.34–0.95; $p = 0.03$). Further, the number of wrist fractures remained low through EXT Yr 6 and the wrist fracture rate continued to remain consistently lower than the Pbo rate observed during FREEDOM (rate ratio = 0.61, 95% CI = 0.39–0.94; $p = 0.025$ compared with FREEDOM).

In untreated women with postmenopausal osteoporosis, cortical bone density at the 1/3 radius declined despite calcium and vitamin D supplementation. DMAb treatment for 3 yrs halted and reversed this bone loss, and additional DMAb treatment resulted in further BMD gains that translated to significantly lower wrist fracture rates through EXT Yr 6. These data provide evidence of a relevant clinical endpoint of reversing cortical bone loss in patients with osteoporosis.

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