Denosumab Decreases Cortical Porosity in Postmenopausal Women With Low Bone Mineral Density

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C Libanati: Amgen employee and shareholder
SK Boyd: Research grants and/or consulting fees from Amgen, Merck, and Servier
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Bone Remodeling & Balance With Aging

Remodeling rate Resorption by BMU Formation by BMU

Serum Calcium and Parathyroid Hormone

Albumin-adjusted Serum Calcium

Parathyroid Hormone

Hypothesis

In the setting of a rapid and marked decrease in bone resorption at tissue and cellular levels produced by denosumab

(i) The increase in PTH is associated with a decrease in cortical porosity
(ii) These associations do not occur with alendronate
**Study Design**
- Multi-center, RDBPC, pilot phase 2, 1-year study
- Ambulatory postmenopausal women, age 50 to 70 yrs, no fractures
- Lumbar spine or total hip T-scores between −2.0 and −3.0
- Randomization 1:1:1 (calcium and vitamin D for all)
- Endpoints assessed using high resolution HR-pQCT (Scanco)

**Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 82)</th>
<th>Alendronate 70 mg QW (N = 82)</th>
<th>Denosumab 60 mg Q6M (N = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)*</td>
<td>60.8 (5.2)</td>
<td>60.7 (5.2)</td>
<td>60.3 (5.9)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)*</td>
<td>26.9 (5.0)</td>
<td>26.4 (4.4)</td>
<td>27.2 (4.3)</td>
</tr>
<tr>
<td>Lumbar spine BMD T-score*</td>
<td>−2.4 (0.3)</td>
<td>−2.5 (0.3)</td>
<td>−2.4 (0.4)</td>
</tr>
<tr>
<td>Total hip BMD T-score*</td>
<td>−1.1 (0.7)</td>
<td>−1.4 (0.7)</td>
<td>−1.4 (0.8)</td>
</tr>
<tr>
<td>Years post menopause*</td>
<td>12.8 (6.2)</td>
<td>13.1 (8.0)</td>
<td>13.6 (7.6)</td>
</tr>
<tr>
<td>Completed study, n (%)</td>
<td>74 (90)</td>
<td>69 (84)</td>
<td>74 (89)</td>
</tr>
<tr>
<td>Discontinued study, n (%)</td>
<td>8 (10)</td>
<td>13 (16)</td>
<td>9 (11)</td>
</tr>
</tbody>
</table>

* mean (SD)

**Porosity**

- % Cortical Porosity
- Rib 6 m
- Rib 12 m
- Vehicle
- ALN
- DMAb
- Transition study

**Cortical Porosity at the Distal Radius**

- % Change From Baseline
- Month 12

**Cortical Porosity at the Distal Radius**

- % Change From Baseline
- Month 12

**PTH, CTX, and P1NP**

- % Change From Baseline
- Month

Seeman et al. *JBMR*. 2010;25:1886

Adapted from Ominsky et al. *JBMR*. 2008;23(S1):S61


Data are least squares means with 95% CIs

Data are means with 95% CIs

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Seeman et al. JBMR 2010;25:1886 and 179 data on file

Seeman et al. JBMR. 2010;25:1886 and 179 data on file
**Summary**

- Denosumab led to BMD gains at the radius compared with baseline, placebo, and alendronate.

- Both alendronate & denosumab produced a transitory increase in PTH.
  - the increase was larger with denosumab.
  - for denosumab the increase occurred after each 6-monthly dose.

- Cortical porosity at 12 months:
  - increased with placebo (+5.2%)
  - increased less with alendronate (+2.9%)
  - decreased with denosumab (−3.0%)

- In the placebo and alendronate groups, increasing PTH was associated with an increase in cortical porosity, whereas in the denosumab group, increasing PTH was associated with a reduction in cortical porosity.

**Limitations**

Porosity is likely to be under-estimated because the automated segmentation method:

1. does not detect low-density cortex
2. does not detect porosity < ~82 µm
3. does not assess the transition zone (with its porosity)

**Inferences**

Denosumab had a positive impact on the cortical compartment and partially reversed micro-architectural deterioration:

(i) directly, by rapidly and markedly reducing remodeling intensity and osteoclast activity,

(ii) perhaps indirectly, by a PTH-dependent effect on BMU level bone formation in the setting of full suppression of osteoclast activity.