Denosumab for Osteoporosis

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Conflicts of Interest

- Research funding, consulting and honoraria from
  - Novartis
  - Amgen
  - AstraZeneca
  - Pfizer
  - Warner Chilcott
  - Sanofi
Denosumab for osteoporosis - outline

• Mechanism of action
• Effect on fracture risk
• Effect on bone turnover and density
• Long-term effect on bone density
• Safety

The characteristics of denosumab and its mechanism of action
Pharmacokinetic and pharmacodynamic properties of Denosumab

- Human monoclonal IgG2 antibody
- Administered via SC injection
  - Dosing schedule: every 6 months (Q6M)
- Reduction in bone turnover markers within 3 days and sustained for up to 6 months
- Maximum serum denosumab after 10 days, and half life is about one month

Tat SK et al. Bone 2006;39:706-715
Denosumab is a RANK Ligand inhibitor and it inhibits osteoclast formation, function, and survival

1. Denosumab binds to and inhibits RANK ligand
2. Denosumab prevents RANK ligand from binding to RANK
3. Denosumab inhibits osteoclast formation
4. Denosumab inhibits osteoclast function and survival

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Bisphosphonates bind to bone and inhibit osteoclasts at the bone surface

1. Bisphosphonates bind to bone and are taken up by mature osteoclasts
2. Bisphosphonates inhibit osteoclast-mediated resorption

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Bisphosphonates and Denosumab are Distributed Differently

Bisphosphonates are adsorbed to bone surfaces at sites of bone turnover¹⁻³

Denosumab circulates in blood and extracellular fluid including bone tissue¹⁴

ALN on bone surfaces at 24 hrs

Control

Denosumab

The effects of Denosumab on vertebral, non-vertebral, and hip fracture in women with osteoporosis

The FREEDOM Trial
Fracture REduction Evaluation of Denosumab in Osteoporosis Every 6 Months
Study design

Phase 3: The FREEDOM Trial

Study population
- 7808 postmenopausal women
- T-score < –2.5 at the lumbar spine or total hip and not < –4.0 at either site
- Exclusion any severe or > 2 moderate vertebral fractures

Primary endpoint
- New vertebral fracture over 36 months

Secondary endpoints
- Non-vertebral fracture
- Hip fracture

Denosumab significantly lowers relative risk of fractures at 36 month

Phase 3: The FREEDOM Trial

ARR = absolute risk reduction; RRR = relative risk reduction
Denosumab is even more effective at reducing non-vertebral fractures in some subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Placebo (N = 3986)</th>
<th>Denosumab (N = 3982)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Interaction P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall FREEDOM Population</td>
<td>8.0% (203/2560)</td>
<td>6.5% (238/3692)</td>
<td>0.80 (0.87, 0.95)</td>
<td>NA</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 75</td>
<td>7.6% (101/1307)</td>
<td>5.9% (150/2567)</td>
<td>0.78 (0.63, 0.96)</td>
<td>0.0621</td>
</tr>
<tr>
<td>≥ 75</td>
<td>9.0% (102/1236)</td>
<td>7.9% (88/11235)</td>
<td>0.84 (0.83, 1.12)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>6.9% (153/1686)</td>
<td>6.2% (98/1603)</td>
<td>0.62 (0.48, 0.80)</td>
<td>0.0434</td>
</tr>
<tr>
<td>25 &lt; T &lt; 30</td>
<td>7.9% (130/1511)</td>
<td>6.9% (150/1190)</td>
<td>0.98 (0.75, 1.30)</td>
<td></td>
</tr>
<tr>
<td>≥ 30</td>
<td>6.0% (204/3410)</td>
<td>6.8% (469/6727)</td>
<td>1.13 (0.71, 1.79)</td>
<td></td>
</tr>
<tr>
<td>Fracture risk RMD T-score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ –2.5</td>
<td>12.3% (159/1269)</td>
<td>8.1% (123/1514)</td>
<td>0.85 (0.51, 1.43)</td>
<td>0.01261</td>
</tr>
<tr>
<td>&gt; –2.5</td>
<td>9.9% (139/1409)</td>
<td>9.9% (128/1486)</td>
<td>0.97 (0.56, 1.69)</td>
<td></td>
</tr>
<tr>
<td>Prevalent vertebral fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9.3% (70/754)</td>
<td>9.6% (84/879)</td>
<td>1.06 (0.78, 1.44)</td>
<td>0.0377</td>
</tr>
<tr>
<td>No</td>
<td>7.7% (209/2736)</td>
<td>5.1% (151/2984)</td>
<td>0.71 (0.58, 0.88)</td>
<td></td>
</tr>
<tr>
<td>Prior nonvertebral fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11.2% (121/1177)</td>
<td>9.4% (103/1103)</td>
<td>0.84 (0.65, 1.09)</td>
<td>0.0682</td>
</tr>
<tr>
<td>No</td>
<td>6.6% (172/2724)</td>
<td>5.3% (135/2537)</td>
<td>0.77 (0.62, 0.97)</td>
<td></td>
</tr>
</tbody>
</table>


Effects of Denosumab on bone mineral density and bone turnover markers

Sheffield Teaching Hospitals
NHS Foundation Trust

The University Of Sheffield
Effect of Antiresorptive Treatment on Bone Turnover Markers: The FREEDOM Trial of Denosumab

Values shown are median (Q1, Q3)

Antiresorptive treatments reduce the level of bone resorption (CTX) and bone formation (PINP) markers (coupling)


Study Design
FREEDOM and FREEDOM EXTENSION studies

An international multi-centre, placebo-controlled study and open-label, single arm extension study to evaluate the long term effect of denosumab on safety, BMDs, BMD, and fracture rates


Preparation date: February 2013
Denosumab in the FREEDOM Extension: Bone Mineral Density

- Women with osteoporosis
- treated with
  - denosumab 60 mg sc, 6-monthly
  - placebo
- Treated for 36 months and then both groups received denosumab


Denosumab in Men: ADAMO

- 228 men with osteoporosis
- treated with
  - denosumab 60 mg sc, 6-monthly
  - placebo
- Treated for 12 months and then both groups received denosumab

Langdahl BL, et al. J Clin Endocrinol Metab. 2015 Apr;100(4):1335-42
Summary of general adverse events (AE) and AE of interest Subject Rates per 100 Patient-years

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Denosumab</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>FREEDOM Years 1-3</td>
<td>FREEDOM Years 1-3</td>
</tr>
<tr>
<td>N = 3883</td>
<td>N = 3879</td>
<td>N = 2343</td>
</tr>
<tr>
<td>Rate (n)</td>
<td>Rate (n)</td>
<td>Rate (n)</td>
</tr>
<tr>
<td>All AEs</td>
<td>156.1 (3614)</td>
<td>154.3 (3598)</td>
</tr>
<tr>
<td>Infections</td>
<td>30.7 (2113)</td>
<td>29.3 (2052)</td>
</tr>
<tr>
<td>Eczema</td>
<td>0.6 (67)</td>
<td>1.1 (119)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>&lt; 0.1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>10.4 (974)</td>
<td>10.6 (1002)</td>
</tr>
<tr>
<td>Infections</td>
<td>1.3 (134)</td>
<td>1.5 (160)</td>
</tr>
<tr>
<td>Cellulitis or Erysipelas</td>
<td>&lt; 0.1 (1)</td>
<td>0.1 (12)</td>
</tr>
<tr>
<td>Fatal AEs</td>
<td>0.8 (90)</td>
<td>0.6 (70)</td>
</tr>
</tbody>
</table>

- ONJ: There were four adjudicated cases of ONJ in the extension study: Two cases in the cross-over and two cases in the continued denosumab group
- Atypical fracture: two cases of atypical femoral fractures have been reported from the FREEDOM Extension trial 20060289

N = Number of subjects who received >/=1 dose of investigational product. Treatment groups are based on the original randomized treatments received in FREEDOM. All subjects in the extension are receiving denosumab; Rate = Exposure-adjusted subject incidence per 100 subject-years; n = Total number of subjects with an adverse event

Adapted from: Papapoulos S, et al. JBMR 2012;27(3):694-701

Osteonecrosis of the jaw - prevention

- A dental examination with appropriate preventive dentistry should be considered prior to treatment with Prolia in patients with concomitant risk factors. While on treatment, these patients should avoid invasive dental procedures if possible.
  - Good oral hygiene practices should be maintained during treatment with Prolia. For patients who develop ONJ while on Prolia therapy, dental surgery may exacerbate the condition. If ONJ occurs during treatment with Prolia, use clinical judgment and guide the management plan of each patient based on individual benefit/risk evaluation.

EMEA, Summary of Product Characteristics, Prolia 2010
Denosumab and hypocalcaemia: importance of caution in chronic kidney disease

Supplementation of calcium and vitamin D is strongly recommended when patients initiate denosumab therapy, particularly in patients with reduced renal function.


Conclusions

- **Mechanism of action**
  - Rapid and potent effect

- **Effect on fracture risk**
  - Reduction in fracture risk, greatest effect at the spine

- **Effect on bone turnover and density**
  - Greater than oral alendronate

- **Long-term effect on bone density**
  - Continued effects to 5 years

- **Safety**
  - Cellulitis; a few cases of ONJ, AFF; transient hypocalcaemia (avoided by administration of calcium and vitamin D supplements)