Denosumab

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NO CONFLICTS OF INTEREST

Bone remodeling is a cellular process

Bone Remodeling

Osteoblasts

Osteoclast

Bone Lining Cells

Osteocytes
3. Osteoprotegerin Prevents RANKL Binding to RANK and Inhibits Osteoclast Activity

- Activated Osteoclast
- Osteoclast Precursor
- Multinucleated Osteoclast
- Colony-Forming Unit-Macrophage
- Osteoblasts

Hormones, Growth Factors, Cytokines


RANKL Signaling

- IFN-γ
- OPG
- RANKL
- RANK
- Stat1
- Stat3
- TRAF6
- c-Fos
- Fra-1, Fra-2
- NF-κB
- JNK
- IFN-β
- IFN-α
- IFN-βR
- ISGF3
- Stat1
- IRF-9

Bone Resorption Inhibited

Denosumab binds to RANKL blocks the production of osteoclasts

- Denosumab
- Osteoclast Formation, Function and Survival Inhibited

Bone Formation

From Bob Josse, Health Plexus 2010
BPs and denosumab act differently

- **Bisphosphonates**
  - BPs bind to bone mineral and are taken up by mature osteoclasts at sites of bone resorption
  - BPs cause loss of resorptive function, but ‘disabled’ osteoclasts

- **Denosumab**
  - Denosumab blocks RANKL
  - Denosumab blocks osteoclast formation, function and

The RANKL/RANK system

- **RANK Ligand (RANKL) circulates**
- **RANK is its transmembrane receptor**
- The interaction of RANK - RANKL interaction is necessary and sufficient for osteoclastic bone resorption

The FREEDOM Trial
denosumab and fracture risk

**Study design:**
- Randomized trial
- Denosumab 60 mg or placebo SC every 6 months for 3 years
- 400-800 IU vit D, 1 g of calcium

**Subjects:**
- 7838 women 60 to 90 years old
- Spine or hip T-score < -2.5

Denosumab Fracture Study

- 7688 women enrolled; 6478 completed 36 mos; 5979 received all injections
- 3902 in denosumab group; 3906 placebo
• Denosumab increased BMD at L-Spine (9.2%) and total hip (6.0%) relative to placebo
• Also significantly decreased CTX and PINP levels vs. placebo
  – "CTX is released directly from bone as a result of osteoclastic resorption"
  – PINP is an osteoblast marker – a marker of bone formation
Denosumab decreased nonvertebral fractures

Denosumab reduced hip fracture risk

Denosumab has similar effects on BMD at all levels of renal function

Denosumab had a greater effect in those with hip BMD T-score <-2.5

- Preplanned analysis
- Overall 20% decrease nonvertebral fractures

Subgroups % decrease (95% CI)
FN BMD T ≤-2.5 35% (27 to 49%)
FN BMD T >-2.5 3% (-23 to 24%)
Interaction P=0.02
FREEDOM - Summary

- Denosumab 60mg SC twice yearly x 36 most significantly reduced the risk of new vertebral fracture compared to placebo
- Also reduced incidence of nonvertebral and hip fractures
- Sig increase BMD at L-spine and total hip
- Sig decrease Bone turnover markers
- Safety signals are minimal at three years

Denosumab and fracture healing

- In the FREEDOM trial, non-union was rare in placebo and denosumab groups
- A sub-study of rate of healing in radius fractures

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 17)</th>
<th>Denosumab (N = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number with evaluable x-rays</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Healed by 6 weeks*</td>
<td>3 (21%)</td>
<td>3 (43%)</td>
</tr>
<tr>
<td>Healed by 3 months*</td>
<td>12 (86%)</td>
<td>6 (86%)</td>
</tr>
<tr>
<td>Healed by 6 months</td>
<td>15 (100%)</td>
<td>7 (100%)</td>
</tr>
</tbody>
</table>
- Effect of Denosumab over 8 years

McClung et al, OI, 2013

Denosumab improves BMD more than does alendronate

Serum CTX

Lewiecki EM et al. J Bone Miner Res. 2007 Dec;22(12):1832-41.
Serum BSAP

BMD declines then recovers

Denosumab and alendronate improved cortical vBMD and thickness

Serum C-telopeptide

The effect of denosumab is reversible
Denosumab increased estimated bending strength more than did alendronate

Polar Moment of Inertia

Distal Radius Cortical Porosity by HRpQCT: 12 months

Cortical Porosity (% change)

- Denosumab (n=82)
  - -2.98

- Alendronate (n=82)
  - +2.66

- Placebo (n=83)
  - +5.19

* p=0.02 vs placebo

Adherence for alendronate weekly vs. denosumab q 6 months

Denosumab and cancer therapies

- Prevents bone loss in women receiving aromatase inhibitors for breast cancer
- Prevents bone loss in men receiving androgen deprivation therapy for prostate cancer
Adverse Events

- No significant difference incidence of serious adverse events
- Specifically no diff in incidence of cancer, CV events, serious infection, delayed fracture healing
- 1 pt developed osteonecrosis of jaw
- Several cases of skin rashes and erysipelas

Clinical Use of Denosumab-Pluses

- Twice per year- good for compliance
- Temporary treatment post anabolic therapy
- Can be used in renal insufficiency- Class III-IV renal dysfunction
- SC use is relatively easy and accessible by primary care
- Can be used in cancer patients
Potential Limitations

- Expense
- Effect wears off after 6 months - what next?
  - If compliance is poor, or if cannot take Rx
  - Is there increased risk of fracture when no Rx is offered
- Biologic - hence long term potential risk?

Summary

- The RANKL/OPG system modulates bone turnover
- RANKL signals through multiple mechanisms - differentiation of osteoclasts
- Monoclonal Ab of RANKL prevents bone resorption and increases bone formation
- Denosumab reduces fractures of the spine and major osteoporotic fractures
- Relatively good safety profile

Weaknesses

- Not blinded
- No mention of race of subjects – most from Europe
- Nonvertebral fractures not evaluated as carefully/objectively as vertebral fractures
- Long term safety not assessed
  - Skin
  - SBE
  - Cancer
- Study supported by Amgen; Most of investigators receiving grants or consulting fees from Amgen
- What happens if people Rxed don’t show up for follow up treatment?
Discussion

- **Bisphosphonate therapy**
  - BPs bind calcium hydroxyapatite and disrupt the survival and function of osteoclasts, thereby reducing bone resorption
  - They do not block the formation of osteoclasts
  - Several clinical trials have shown that BP therapy leads to a 33-60% reduction in risk of fractures
  - SEs (esp with oral BPs which are poorly absorbed) can be intolerable: dysphagia, esophagitis, risk of osteonecrosis of the jaw and delayed fracture healing

Strengths

- Relatively large sample size
- Randomized, placebo-controlled
- Groups not sig different
- Spine XRs assessed by semi-quantitative grading scale at central imaging center
- 3 year study, follow-up still ongoing

Denosumab

- By blocking binding of RANKL and RANK, denosumab inhibits bone resorption by osteoclasts and inhibits formation of new osteoclasts from osteoclast precursors
**Denosumab: Overview**

- Fully human monoclonal antibody-IgG$_2$ isotype
- High affinity and specificity for human RANK Ligand
- Pharmacokinetics (SC): similar to other fully human IgG$_2$ monoclonal antibodies
  - Absorption is rapid and prolonged ($C_{\text{max}} \approx 1-4$ wks postdose)
  - Long half-life $\approx 34$ days with max dose
  - Distribution $\approx$ intravascular volume
  - Clearance $\approx$ reticuloendothelial system
  - No kidney filtration or excretion of intact molecule

**Early Studies**

- Previous studies have demonstrated increased BMD and decreased bone turnover with use denosumab
  - McClung 2006: phase II trial of efficacy and safety of different doses and frequencies of denosumab over 12 months in 400+ postmenopausal women with low BMD
  - Compared to placebo and alendronate
  - Denosumab increased BMD, decreased markers of bone turnover better than placebo and as effectively as alendronate

**Previous Studies**

- Brown et al 2006 compared BMD and BTMs in Denosumab vs. Alendronate
  - 1100+ postmenopausal women with low BMD ($T<-2.0$) treated for 1 year
  - Sig greater increases in BMD in D vs A
  - BTMs decreased more in D vs A
  - Not powered to assess risk of fracture b/t groups
Denosumab Phase 2 Study


- 2-year data: J Bone Miner Res 2007

- 4-year data: ASBMR Oral Presentation 2007

Spine BMD

![Graph showing Spine BMD change over time](Lewiecki EM et al. J Bone Miner Res. 2007 Dec;22(12):1832-41.)

Total Hip BMD

![Graph showing Total Hip BMD change over time](Lewiecki EM et al. J Bone Miner Res. 2007 Dec;22(12):1832-41.)
**Denosumab**

- Denosumab is a “fully-human” monoclonal antibody that binds to RANKL.
  - **RANKL** - a ligand for RANK (receptor found on osteoclasts) which promotes function, formation and survival. Found on T cells, marrow stromal cells and precursors to osteoblasts.
  - **Osteoprotegerin** is the endogenous modulator of RANKL, blocking its effects.
  - Denosumab mimics osteoprotegerin.

**Results**

- Cumulative incidence of nonvertebral fracture: 6.5% (D) vs. 8.0% (P)
  - 20% RRR
- Cumulative incidence of hip fracture: 0.7% vs. 1.2%
  - 40% RRR
  - Diff in rates here not stat sig; small number of subjects getting hip fractures in the study.
Figure 2: Percent Change in Total Hip BMD From Parent Study Baseline

Parent Study (0–48 months)  Extension Study (48–96 months)

Results are based on available data at time of submission. Data are least squares mean (95% CI). N = number of subjects with parent study baseline (BL) and ≥1 post-BL measurement.

McClung et al, JBMR, 2011