Creating New Bone:
Use of Anabolic Agents

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Disclosures

I am disclosing financial relationships as follows:

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Honorarium for speaking: Amgen, Radius

Michael McClung, MD 2017
Osteoporosis: Definition and Pathogenesis

**Definition**

A disorder due to bone loss that damages skeletal architecture, weakens the skeleton and predisposes a patient to fracture

- *a combination of low bone mass and damaged microarchitecture*

**Pathogenesis**

Imbalance in bone remodeling such that rate of resorption exceeds that of formation

Images Courtesy of Drs. David Dempster, Roger Zebazi and Sergio Ragi
Bone Remodeling

Osteoclasts remove old bone, osteoblasts make new bone & osteocytes sense mechanical stress and direct the activity of ‘clasts & ‘blasts.

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Effects of Treatments on Remodeling

Alendronate
Anti-remodeling agent

Teriparatide
Remodeling stimulator

Bone Growth

- In vivo micro computed tomography of growing rat tibia.

Bone Modeling

Activation of lining cells

Adapted from Seeman E and Delmas PD; *N Engl J Med* 2006; 354:2250-61
Anabolic Effects of PTH

Adapted from Seeman E and Delmas PD; *N Engl J Med* 2006; 354:2250-61
Teriparatide-induced Bone Formation

Remodeling based

Modeling based

Effects of Teriparatide on Bone Structure

- Teriparatide – increases bone formation and resorption

*Improved trabecular bone mass, strength and structure*

Effects of Teriparatide on Bone Structure

- Teriparatide – increases bone formation and resorption

*Improved trabecular bone mass, strength and structure*

*In cortical bone, teriparatide*
  - increases cortical porosity
  - increases cortical thickness
  - improves hip strength

Teriparatide: Bone Formation in Femoral Neck

Teriparatide: Effects on Fracture Risk

Postmenopausal women with previous vertebral fracture followed for ~19-21 months \(^1\)

**Placebo group**

<table>
<thead>
<tr>
<th>Fracture type</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphometric vertebral</td>
<td>14 %</td>
</tr>
<tr>
<td>Non-vertebral fragility</td>
<td>6%</td>
</tr>
</tbody>
</table>

**Teriparatide 20 ugm daily**

<table>
<thead>
<tr>
<th>Fracture type</th>
<th>RRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphometric vertebral</td>
<td>65%</td>
</tr>
<tr>
<td>&gt;1 moderate or severe</td>
<td>90%</td>
</tr>
<tr>
<td>Non-vertebral</td>
<td>35%</td>
</tr>
</tbody>
</table>

Severity of vertebral fractures reduced \(^2\)

New Anabolic Agents

- **Abaloparatide**
  - Analog of PTHrP
  - Compared to teriparatide
    - Less activation of bone remodeling than teriparatide
    - Somewhat greater increases in BMD
    - Fracture risk reduction at least as good

New Anabolic Agents

- **Abaloparatide**
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- **Romosozumab**
  - Inhibits sclerostin
  - Marked but transient increase in bone formation
  - Decreased bone resorption

Abaloparatide
Phase 3 Extension Study (ACTIVE)

Total hip BMD
Lumbar spine BMD

Miller PD et al. JAMA. 2016;316:722-33
Sclerostin Inhibitor: Romosozumab

Phase 2 Study: Bone Mineral Density

Data are LS means and 95% CIs.

Romosozumab Phase 2 Study: Year 3 - BMD
Romosozumab Discontinuation: Transition to Denosumab

Percent Change from Baseline

Lumbar Spine

- Romosozumab 210 mg QM*
- Denosumab 60 mg Q6M
- Placebo*
- Placebo Q6M

Total Hip

New Anabolic Therapies: 
*Phase 3 Study Designs*

**ACTIVE - abaloparatide**

- **Abaloparatide**: 18 Months
- **Alendronate**: 36 Months


**FRAME - romosozumab**

- **Romosozumab**: 12 Months
- **Denosumab**: 24 Months

Abaloparatide
Phase 3 Extension Study (ACTIVE)

Miller PD et al. JAMA. 2016;316:722-33
Abaloparatide
Phase 3 Extension Study (ACTIVExtend)

April 28, 2017: FDA approved as treatment for women with postmenopausal osteoporosis at high risk for fracture
Abaloparatide
Phase 3 Extension Study (ACTIVExtend)
Sclerostin Inhibitor: Romosozumab

Phase 3: FRAME: Vertebral Fracture Risk Reduction

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romosozumab</td>
<td>Denosumab</td>
</tr>
<tr>
<td>Placebo</td>
<td>Denosumab</td>
</tr>
</tbody>
</table>

ClinicalTrials.gov Identifier: NCT01575834

Sclerostin Inhibitor: Romosozumab
*Phase 3: FRAME: Vertebral Fracture Risk Reduction*

**Year 1**
- Romosozumab
- Placebo

**Year 2**
- Denosumab
- Denosumab

*ClinicalTrials.gov Identifier: NCT01575834*

All patients on denosumab 60 mg Q6M

Sclerostin Inhibitor: Romosozumab

Phase 3: FRAME: BMD

# Total Hip BMD Responses to Osteoporosis Therapies

1 T-score = 12% of young normal values

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial</th>
<th>18 MO</th>
<th>24 MO</th>
<th>36 MO</th>
<th>48 MO</th>
<th>8-9 YR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid</td>
<td>HORIZON</td>
<td>~3%*</td>
<td>-</td>
<td>4%</td>
<td>-</td>
<td>4.6%</td>
</tr>
<tr>
<td>Denosumab</td>
<td>FREEDOM</td>
<td>~4%*</td>
<td>-</td>
<td>5.5%</td>
<td>-</td>
<td>8.3%</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>PFT (Neer)</td>
<td>2.6%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Teriparatide + denosumab</td>
<td>DATA</td>
<td>-</td>
<td>6.3%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Teriparatide to denosumab</td>
<td>DATA</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6.6%</td>
</tr>
<tr>
<td>Teriparatide + denosumab to denosumab</td>
<td>DATA</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8.8%</td>
<td>-</td>
</tr>
<tr>
<td>Abaloparatide</td>
<td>ACTIVE</td>
<td>4.2%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Abaloparatide to alendronate</td>
<td>ACTIVE</td>
<td>-</td>
<td>5.5%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Romosozumab – 12 months</td>
<td>FRAME</td>
<td>6.9%*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Romosozumab to denosumab</td>
<td>FRAME</td>
<td>-</td>
<td>8.8%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

** data at 12 months
Anabolic Therapy for Postmenopausal Osteoporosis: Summary

Where will anabolic therapy be used?

- For patients at high risk for fracture in need of skeletal reconstruction, beginning anabolic therapy followed by an anti-remodeling agent will become standard practice.

  - patients at imminent risk for vertebral fracture, especially those with recent vertebral fracture.

  - patients with very low hip BMD in whom anti-remodeling therapy will never achieve a BMD target.

M McClung. Personal opinion
Anabolic Therapy: Beyond Postmenopausal Osteoporosis

**States of impaired bone formation**

- Long-term glucocorticoid therapy
  
  *Here there is evidence of superiority of teriparatide vs alendronate*[^2]
- Idiopathic osteoporosis of young adults
- Immobilization
- Adynamic bone disease in chronic renal failure
- Eating disorders
- Genetic disorders of bone formation
  - *Teriparatide increases BMD in adults with osteogenesis imperfecta*[^3]
- Impaired fracture healing

[^1]: M McClung. Personal opinion
Thank you