New Approaches to Treating Osteoporosis

Northern California Institute for Bone Health
Annual Education Meeting
Oakland, CA
May 20, 2016

Michael R. McClung, MD
Director, Oregon Osteoporosis Center
Portland, Oregon, USA

Disclosure and Conflicts of Interest

I serve on Advisory Boards of Amgen, Merck and Radius and have received honoraria from Amgen and Merck

Michael McClung, MD 2016

Osteoporosis Treatment: Benefits

- Many of our current drugs are very effective for treating osteoporosis
  - Vertebral fracture by 60-70%
  - Hip fracture by 40-60%
  - Non-vertebral fracture by 20-35%
- In general are well tolerated
- In clinical trials, have been very safe

Osteoporosis Treatment: Limitations

- Real or perceived intolerance
- Concerns about safety, especially the long-term safety of bisphosphonates
- Inconvenient or awkward dosing regimens
- Poor adherence to therapy
- No agent restores skeletal structure or strength to normal levels
  - i.e., no “cure” for osteoporosis
- Expense

On and Over the Horizon: Future Treatments

Anti-resorptive agents
  - New estrogen agonists/antagonists (EAAs)
  - Oral calcitonin
  - Cathepsin K inhibitors

Anabolic agents
  - New analogs of PTH
  - Calcilytics
  - Biological activators of bone formation
  - Anti-sclerostin antibody
  - DKK inhibitors

Treatments for Osteoporosis are Based on Bone Remodeling
Bone Remodeling

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

Bone Remodeling

PTHrP and Abaloparatide

- PTH and PTHrP bind to same PTH receptor — but kinetics of effects after activation are very different: much longer with teriparatide vs PTHrP 1-36
- PTHrP 1-36:
  - Phase 1 studies: PTHrP(1-36) increased markers of bone formation but had little effect on bone resorption and did not cause hypercalcemia.
  - Phase 2 study — vs teriparatide:
    - Smaller increases in markers of bone formation and resorption
    - Minimal differences in BMD response
    - Same or more hypercalcemia

Abaloparatide: Synthetic Analogue of Human PTHrP 1-34

hPTH₁-34

hPTHrP₁-34

PTHRP analog (BA058)

100% hPTHrP
38% hPTHrP

Functional optimization of BA058 based on amino acids 22-34
More selectively binds to R*G PTH receptor than does PTHrP

Abaloparatide vs Teriparatide

Change in Spine BMD over 12 Months

Hypercalcemia (%)

Placebo 4%
TPTD 40%
PTHrP 80 ugm 18%

Abaloparatide vs Teriparatide

Change in Biomarkers at 6 Months

Women with postmenopausal osteoporosis
Interventions:
- PTHrP 20, 40 or 80 ugm QD
- TPTD 20 ugm QD
- Placebo

Abaloparatide vs Teriparatide

Change in Spine BMD over 12 Months

Lumbar Spine BMD

% change from baseline

Abaloparatide: Pivotal Phase 3 Study Design

Bone Remodeling

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

OOC


OOC

Bone Remodeling

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

OOC


OOC


Abaloparatide: Synthetic Analogue of Human PTHrP 1-34

hPTH₁-34

hPTHrP₁-34

PTHRP analog (BA058)

100% hPTHrP
38% hPTHrP

Functional optimization of BA058 based on amino acids 22-34
More selectively binds to R*G PTH receptor than does PTHrP

Abaloparatide vs Teriparatide

Change in Biomarkers at 6 Months

Women with postmenopausal osteoporosis
Interventions:
- PTHrP 20, 40 or 80 ugm QD
- TPTD 20 ugm QD
- Placebo

Abaloparatide vs Teriparatide

Change in Spine BMD over 12 Months

Hypercalcemia (%)

Placebo 4%
TPTD 40%
PTHrP 80 ugm 18%

Abaloparatide vs Teriparatide

Change in Spine BMD over 12 Months

Lumbar Spine BMD

% change from baseline

Abaloparatide: Pivotal Phase 3 Study Design

Bone Remodeling

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

OOC


OOC


OOC


Abaloparatide: Synthetic Analogue of Human PTHrP 1-34

hPTH₁-34

hPTHrP₁-34

PTHRP analog (BA058)

100% hPTHrP
38% hPTHrP

Functional optimization of BA058 based on amino acids 22-34
More selectively binds to R*G PTH receptor than does PTHrP

Abaloparatide vs Teriparatide

Change in Biomarkers at 6 Months

Women with postmenopausal osteoporosis
Interventions:
- PTHrP 20, 40 or 80 ugm QD
- TPTD 20 ugm QD
- Placebo

Abaloparatide vs Teriparatide

Change in Spine BMD over 12 Months

Hypercalcemia (%)

Placebo 4%
TPTD 40%
PTHrP 80 ugm 18%

Abaloparatide: Pivotal Phase 3 Study Design

Bone Remodeling

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

OOC


OOC


OOC


Abaloparatide: Synthetic Analogue of Human PTHrP 1-34

hPTH₁-34

hPTHrP₁-34

PTHRP analog (BA058)

100% hPTHrP
38% hPTHrP

Functional optimization of BA058 based on amino acids 22-34
More selectively binds to R*G PTH receptor than does PTHrP

Abaloparatide vs Teriparatide

Change in Biomarkers at 6 Months

Women with postmenopausal osteoporosis
Interventions:
- PTHrP 20, 40 or 80 ugm QD
- TPTD 20 ugm QD
- Placebo

Abaloparatide vs Teriparatide

Change in Spine BMD over 12 Months

Hypercalcemia (%)

Placebo 4%
TPTD 40%
PTHrP 80 ugm 18%

Abaloparatide: Pivotal Phase 3 Study Design
ACTIVE Trial: Abaloparatide vs Teriparatide

**Bone Mineral Density**

- 2460 women with postmenopausal osteoporosis
- Interventions:
  - Abaloparatide 80 ugm QD
  - Teriparatide 20 ugm QD
  - Placebo

**Relative Risk Reduction**

- 78%
- 83%

ACTIVE Trial: Abaloparatide vs Teriparatide

**Morphometric Vertebral Fractures (new and worsening)**

- Interventions:
  - Abaloparatide 80 ugm QD
  - Teriparatide 20 ugm QD
  - Placebo

**Non-vertebral Fractures**

- Placebo
- Teriparatide
- Abaloparatide

**Adverse Events of Interest**

<table>
<thead>
<tr>
<th></th>
<th>Placebo N = 820 (%)</th>
<th>Abaloparatide N = 822 (%)</th>
<th>Teriparatide N = 818 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back pain</td>
<td>10.0%</td>
<td>8.6%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>8.9%</td>
<td>10.9%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>1.2%</td>
<td>6.0%</td>
<td>10.8%</td>
</tr>
</tbody>
</table>

**Abaloparatide: Future Use**

- Will be used like teriparatide (TPTD)
- Its specific role will be determined by
  - More careful analysis of non-vertebral fracture data vs TPTD
  - Convenience of dosing vs TPTD
  - Cost relative to TPTD

**Combined Denosumab and Teriparatide**
Combined Denosumab and Teriparatide

No or minimal additional increment in BMD during year 2 with combined vs monotherapy.

- Concurrent use of teriparatide with denosumab results in faster and modestly greater increases in BMD than with either drug alone.

- This effect occurs because the inhibition of bone formation with denosumab is blunted by co-administration of PTH, i.e., less inhibition of bone formation with combined therapy vs denosumab—but the increase in bone formation with teriparatide is not apparent.


Cathepsin K Inhibition

Cathepsin K is highly expressed in the osteoclast. Localized in the lysosomes and released during bone resorption.
Cathepsin K and Bone: Genetics

- Genetic deficiency - Pycnodysostosis (Gebb, et al., 1996; Schilling et al 2007)
  - short stature, high bone mass
  - skeletal fragility in homozygotes
- Cathepsin K (Cat K) deficient mice (Pennypacker et al, 2009)
  - osteopetrosis
  - increased bone formation
- Over-expression of Cat K (Kiviranta et al, 2001)
  - osteopetrosis
  - increased bone turnover and osteopenia

Odanacatib

- a non-lysosomotropic reversible CatK inhibitor
  - highly selective for CatK in vitro and in vivo
- very strong preclinical evidence
  - inhibition of bone resorption
  - variable effects on bone formation

Odanacatib Preserves Bone Formation while Inhibiting Bone Resorption: Preclinical Evidence

- Odanacatib reduces the activity of cathepsin K in osteoclasts
  - Same number of resorption pits, but shallower
- Allows subsequent bone formation

Odanacatib Increases Periosteal Bone Formation in Ovariectomized Monkeys

- ODN effects on bone formation are site specific:
  - Trabecular surface of spine, ODN dose-dependently inhibited BFR
  - At proximal femur, ODN increased endocortical and periosteal bone formation

Odanacatib Increases Cortical Thickness and Strength in Femur of O VX Monkeys

• Phase II: 3-50 mg once weekly vs placebo
  • dose-dependent increase in BMD
  • inhibited resorption more than formation
  • rapid off effect when treatment stopped
**Odanacatib: Clinical Trials**

- Phase III (LOFT): 50 mg once weekly vs placebo
  - 16,371 women with osteoporosis randomized
  - event driven trial
  - halted after first planned interim analysis
  - mean duration of exposure – 34 months (0-58)
  - this is primary analysis

  - continued original treatment for full 5 years
  - completed March 2015
  - open-label extension out to 10 years

**Odanacatib: Effect on Fracture Risk**

- In LOFT study, odanacatib 50 mg po once weekly significantly reduced fracture risk in women with osteoporosis

  - Relative risk reduction (%), 95% (confidence interval)
    - spine 54% (2.3% vs 7.2%)
    - hip 47% (0.7% vs 1.2%)
    - non-vertebral * 23% (6.5% vs 8.0%)

  * Time-dependent decrease in non-vertebral fracture risk
Odanacatib: Safety

- Generally well tolerated
- Very small number of patients with
  - morphea-like skin lesions without systemic features
    - (5/10,000 pt-yr)
  - femoral shaft fractures with some atypical features
    - (2/10,000 pt-yr)
- Small numerical differences in atrial fibrillation (more) and MIs (less) in ODN treated patients
- Imbalance in adjudicated strokes and fatal strokes
  - but adjudication was incomplete

Odanacatib: Future Use

- May well be a first line, long-term therapy
- ?combination with an anabolic agent during year 1
- Its role will be determined by final results of safety analyses from Phase 3 study

Sclerostin Inhibition

- Sclerostin - an inhibitor of Wnt signaling in osteoblasts
- Mechanical Load
- Altered transcription of several genes
- Enhanced bone formation

Sclerosteosis

- Increased bone mass throughout skeleton.
- Very low fracture risk
- due to absence of sclerostin (SOST) - a bone formation inhibitor

Anti-sclerostin Antibody Therapy in Rats

- Rats ovariectomized at age 6 months.
- Treatment for 5 weeks beginning at 13 months of age
- Results are DDX measurements of lumbar spine and femur-tibia
  - Mean of 11-12 animals ± SE
  - ↑ 26% in spine and 17% in leg

Increased bone mass throughout skeleton.

Sclerosteosis / van Buchem's

Normal Sclerosteosis

Photo: Janssens and Van Hul

Rats ovariectomized at age 6 months.

Treatment for 5 weeks beginning at 13 months of age

Results are DXX measurements of lumbar spine and femur-tibia

- Mean of 11-12 animals ± SE
- ↑ 26% in spine and 17% in leg
Sclerostin Antibody Therapy in Rats

Rats ovariectomized at age 6 months.
Treatment for 5 weeks beginning at 13 months of age
3D µCT images of distal femur at end of study

OCC


Sclerostin Antibody Increases Cancellous Bone Volume and Bone Formation

L2 VERTEBRA

PROXIMAL TIBIA

OCC


Sclerostin Antibody Therapy in Rats

VEHICLE           Scl-AbIV (30 mg/kg)

L2 VERTEBRA

PROXIMAL TIBIA

VEHICLE           Scl-AbIV (30 mg/kg)

Cynomolgus monkeys treated for 10 weeks with sclerostinAb

OCC


Romosozumab (Humanized Anti-sclerostin Antibody)

Bone Markers: Phase 1

Romosozumab Phase 2 Study: Bone Mineral Density

Lumbar Spine

Total Hip

Romosozumab Phase 2 Study

Serum P1NP and CTX

Bone Mineral Density – Year 2

Continued Romosozumab Therapy


McClung MR et al. ASBMR 2014.

OCC

**Bone Mineral Density – Year 3**

*Romosozumab Discontinuation: Transition to Denosumab*

<table>
<thead>
<tr>
<th>Month</th>
<th>Total Hip</th>
<th>Lumbar Spine</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>36</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>18</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>12</td>
<td>-5</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>-8</td>
</tr>
</tbody>
</table>

**Anti-sclerostin Therapy**

*Phase III studies are underway*
- Unique mechanism of action
- Longer duration of “anabolic window”
- Possibility of “cure” with short-term treatment
- Caveat: Tissue specificity is required (stimulation of only bone formation)
- Could be a first line therapy in patients with severe osteoporosis

**Phase 3 FRAME Study**

*Top-line Results*
- Year 1: romosozumab 210 mg Q month vs placebo
- Year 2: open label denosumab 60 mg Q 6 months
- At 12 months
  - 73% reduction in vertebral fracture risk
  - 36% reduction in clinical fracture risk
  - Non-vertebral fracture risk not significantly reduced
- At 24 months
  - 75% reduction in vertebral fracture risk
  - Clinical and non-vertebral fracture risk not significantly different between treatment groups

**Anti-sclerostin Therapy: Future Use**
- Will be used to treat patients with severe osteoporosis
- Will be used sequentially with anti-remodeling drugs

**Osteoporosis Treatment: – 2016**
- We have very effective tools for identifying patients at high risk of fracture
- We have several classes of effective treatments to prevent bone loss and to reduce fracture risk
- New drugs are in development – some may actually “cure” osteoporosis
- Biggest challenge is to implement these tools and strategies effectively
Thank you

Working to prevent
Bone Attacks
OREGON OSTEOPOROSIS CENTER

Michael R. McClung, MD, FACP
Founding Director
Oregon Osteoporosis Center
Portland, Oregon, USA
mmcclung@orost.com