What’s New and On the Horizon for Prescription Medicines

North American Menopause Society
Las Vegas, NV
October 1, 2015
Michael R. McClung, MD, FACP
Director, Oregon Osteoporosis Center
Portland, Oregon, USA

Images Courtesy of Dr. David Dempster

Disclosure and Conflicts of Interest

I serve on the Global Advisory Boards of the following companies:
Amgen, Lilly, Merck

I receive honoraria from the following companies:
Alexion, Amgen, GSK and Merck

Michael McClung, MD 2015

Current Osteoporosis Treatments: 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

Emerging Treatments

Anti-resorptive agents
Cathepsin K inhibitors

Anabolic agents
New analogs of PTH
Biological activators of bone formation
Anti-sclerostin antibody
**PTHrP**

- PTH and PTHrP bind to same PTH receptor – but kinetics of effects are different: much longer with teriparatide vs PTHrP 1-36. This may account for greater effects on bone resorption and calcium mobilization.
- 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
- hPTHrP 1-34
- 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: Phase 2 Studies**

- Compared to 20 ugm teriparatide daily, 80 ugm abaloparatide daily resulted in
  - Smaller increases in markers of bone formation and especially of bone resorption
  - Larger increases in spine and especially hip BMD
  - Lower frequency of hypercalcemia

*Daily subcutaneous dosing was well tolerated*

Abaloparatide: Pivotal Phase 3 Study Design (ACTIVE)

A Randomized, Double-blind, Placebo-controlled, Comparative Phase 3 Multicenter Study to Evaluate the Safety and Efficacy of Abaloparatide for Prevention of Fracture in Postmenopausal Women with Severe Osteoporosis and at Risk of Fracture

**Horwitz MJ et al. J Bone Miner Res. 2013; 28:2266-76.**

**Hattersley R et al. Endocrine Society. OR31-5, 2014.**

**Hattersley R et al. Endocrine Society. OR-08, 2012.**

**Leder BZ et al. J Clin Endocrinol Metab. 2015;100:697-706.**

**Radius Health Form 8-K: January 12, 2015.**
ACTIVE Trial: Abaloparatide vs Teriparatide

Bone Mineral Density – 18 Months

2460 women with postmenopausal osteoporosis

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

PLACEBO 0 4 8 12 % Change from baseline

Lumbar spine

TPTD-20

Abaloparatide 80 ugm QD

Teriparatide 20 ugm QD

Placebo

ANOVA approach

P=0.016

ACTIVE Trial: Abaloparatide vs Teriparatide

Morphometric Vertebral Fractures (worsening and/or new)

Evaluable patients at 18 months

Placebo N = 820
Abaloparatide N = 822
Teriparatide N = 818

Fracture rate (RRR) \(^1\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>Abaloparatide</th>
<th>Teriparatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (evaluable)</td>
<td>711</td>
<td>690</td>
<td>717</td>
</tr>
<tr>
<td>Fracture rate (RRR) (^1)</td>
<td>4.36%</td>
<td>0.72% (83%)</td>
<td>0.98% (78%)</td>
</tr>
</tbody>
</table>

RRR = Relative risk reduction

ACTIVE Trial: Abaloparatide vs Teriparatide

Non-vertebral Fractures

Log-rank p-values:
- Abaloparatide vs Placebo: 0.0489
- Teriparatide vs Placebo: 0.2127
- Abaloparatide vs Teriparatide: 0.4363

RRR = Relative risk reduction

ACTIVE Trial: Abaloparatide vs Teriparatide

Adverse Events of Interest

<table>
<thead>
<tr>
<th>Event</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>

Overall effect on fracture risk did not differ significantly between active treatment groups, but the reduction in risk appeared to occur earlier with abaloparatide.
Abaloparatide: Future Use

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

M McClung. Personal opinion

Cathepsin K Inhibitors
Odanacatib

- Cathepsin K is major osteoclast-derived protease
- Genetic deficiency causes osteocyte-rich osteosclerosis with decreased resorption but formation is present
- Odanacatib is a non-lysosomotropic selective inhibitor of CatK
- Very strong pre-clinical program
  - Decreased resorption but no change or even increase in numbers of osteoclast
  - Increased periosteal formation
  - Increased cortical bone thickness and strength

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

Effects of Odanacatib on 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

OOC
Odanacatib: Effect on Fracture Risk

- In LOFT study of more than 16,000 women with postmenopausal osteoporosis, odanacatib 50 mg po once weekly significantly reduced fracture risk

- Relative risk reduction % (ODN vs PBO)
  - vertebral 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

- Final safety data are being adjudicated
- Results of the full 5 year blinded extension study will be available shortly
- Regulatory filing anticipated soon.
What Will Odanacatib Offer?

- First line treatment or most patients with osteoporosis
- Unique mechanism of action
- anti-resorptive with minimal effect on formation
- indirect anabolic agent
- Better efficacy - possibly
- Different tolerability and safety profile
- Possible combinations with anabolic agents

M McClung. Personal opinions

Anti-sclerostin Therapy

- Sclerostin is an osteocyte-derived inhibitor of Wnt signaling in osteoblasts, resulting in decreased bone formation
- Sclerostin-deficient adults with sclerostosis or Van Buchem’s disease present with high bone mass of excellent quality
- Heterozygotes of these conditions normal phenotype except high bone
- In animals, anti-sclerostin antibodies promote new bone formation, normalizing bone mass, structure and strength


Romosozumab Phase 2 Study: Bone Mineral Density

![Graph showing percentage change from baseline for Lumbar Spine and Total Hip.]

Romosozumab Phase 2 Study Serum P1NP and CTX

![Graph showing percentage change from baseline for P1NP and CTX.]

Except for Week 1, all values were collected pre-dose


Except for Week 1, all values were collected pre-dose

**Blosozumab Phase 2 Study**

**Lumbar Spine and Total Hip BMD**

- **Lumbar Spine**
  - Blosozumab 270 mg Q2W: +17.7% (95% CI)
  - Blosozumab 180 mg Q2W: +8.4% (95% CI)
  - Blosozumab 180 mg Q4W: +2.1% (95% CI)
  - Placebo: -0.1% (95% CI)

- **Total Hip**
  - Blosozumab 270 mg Q2W: +6.3% (95% CI)
  - Blosozumab 180 mg Q2W: +4.2% (95% CI)
  - Blosozumab 180 mg Q4W: +2.7% (95% CI)
  - Placebo: -0.7% (95% CI)

**Bone Mineral Density – Year 2**

**Continued Romosozumab Therapy**

- **Lumbar Spine**
  - Romosozumab 210 mg QM: +15.7% (95% CI)
  - Denosumab 60 mg Q6M: +15.4% (95% CI)
  - Placebo: -0.4% (95% CI)

- **Total Hip**
  - Romosozumab 210 mg QM: +4.2% (95% CI)
  - Denosumab 60 mg Q6M: +5.0% (95% CI)
  - Placebo: -1.5% (95% CI)

**Bone Mineral Density – Year 3**

**Romosozumab Discontinuation: Transition to Denosumab**

- **Lumbar Spine**
  - Romosozumab 210 mg QM: +10.3% (95% CI)
  - Denosumab 60 mg Q6M: +9.5% (95% CI)
  - Placebo: +0.4% (95% CI)

- **Total Hip**
  - Romosozumab 210 mg QM: +6.4% (95% CI)
  - Denosumab 60 mg Q6M: +7.1% (95% CI)
  - Placebo: +0.4% (95% CI)

**Anti-sclerostin Therapy**

**Phase III studies are underway**
- Evaluation of safety will be important

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3 extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denosumab</td>
<td>Denosumab</td>
<td>Denosumab</td>
</tr>
<tr>
<td>Placebo</td>
<td>Denosumab</td>
<td>Denosumab</td>
</tr>
</tbody>
</table>

ClinicalTrials.gov Identifier: NCT01575834

ClinicalTrials.gov Identifier: NCT01631214


McClung MR et al. ASBMR 2014.
New Prescription Therapy: Summary

- Advances in understanding of the molecular regulation of bone metabolism have provided exciting new therapeutic possibilities.
- We are entering a new phase in the treatment of osteoporosis in which new therapies will improve the balance of bone metabolism and may be able to restore skeletal mass, architecture and strength in patients with severe osteoporosis.

Images courtesy of Dr. David Dempster.