Teriparatide, alone and in combination with antiresorptives

Anne Schafer, MD
Assistant Professor
Medicine - Endocrinology & Metabolism
Epidemiology & Biostatistics

I have nothing to disclose.

Outline
- Overview of anabolic therapy
  - Currently FDA-approved: Teriparatide
- Combining anabolic and antiresorptive therapies

Treatment of Osteoporosis
- Antiresorptive agents
  - Bisphosphonates (oral or IV)
  - Raloxifene
  - Estrogen
  - Calcitonin
  - Denosumab
- Anabolic agents
  - Teriparatide
Anabolic therapy increases bone remodeling

Parathyroid Hormone (PTH)
- 84 amino acid sequence
- Most of bone activity in first 34 amino acids
  - PTH (1-34) (teriparatide) approved @ 20 mcg/day
  - PTH (1-84) not approved in US for osteoporosis
- Requires (currently) daily injection
  - Subcutaneous, abdomen

PTH (1-34) (Teriparatide)
Fracture Prevention Trial
- 1637 postmenopausal women
- Randomized to placebo, PTH (1-34) 20 ug, or PTH (1-34) 40 ug
- Fracture was primary endpoint
- 3-year study, halted after 21 months (median)
  - Safety problem with high doses in rodents

Neer, NEJM, 2001

PTH increases bone formation before bone resorption

Black, NEJM, 2003
(adapted from Canalis, NEJM, 2007)
Effect of teriparatide on spine BMD

- Placebo
- PTH 20 mcg
- PTH 40 mcg

% Change (± SE)

- 0
- 2
- 4
- 6
- 8
- 10
- 12
- 14
- 16

*** p < 0.001 vs. Placebo

Neer, NEJM, 2001

Effect of teriparatide on total hip BMD

- Placebo
- PTH 20 mcg
- PTH 40 mcg

% Change (± SE)

- ~ 2%

*** p < 0.001 vs. Placebo

Neer, NEJM, 2001

Effect of teriparatide on incident vertebral fracture risk

RR 0.35 (95% CI, 0.22 to 0.55) *P < 0.001

Neer, NEJM, 2001

Effect of teriparatide on non-vertebral fracture risk

(Adapted from Neer, NEJM, 2001)
Histomorphometry: Teriparatide in a 64 y.o. woman

Dempster, J Bone Miner Res, 2001

Teriparatide in clinical practice

- Approved for up to 2 years duration
- Limited adoption in clinical practice
  - Cost (>10,000/course)
  - Need for daily injections

Teriparatide in clinical practice

- High risk for future fracture
  - Prevalent vertebral compression fx
  - Other osteoporotic fx + low BMD
  - Very low BMD (e.g., T-score <-3.0)
- Failed antiresorptive therapy
  - Incident fx or active bone loss
  - Glucocorticoid-induced osteoporosis

Combination PTH + antiresorptive?

- PTH increases formation then resorption
- Antiresorptives decrease resorption then formation
  - Combine PTH with antiresorptives to increase formation with smaller increase in resorption?
  - Could be synergistic: 1 + 1 = 3
  - Or cancel each other: 1 - 1 = 0
3 distinct possibilities

1. Antiresortive → PTH

2. Antiresortive + PTH

3. PTH → Antiresortive

**Combination #1**

- Pre-treatment with antiresorptives followed by PTH
  - Key clinical question
  - Many patients on bisphosphonates and other antiresorptives

**Combination #2**

- Concurrent initiation of PTH plus antiresorptive in treatment naïve women
  - PTH+alendronate
  - PTH+zoledronic acid
  - PTH+denosumab

**PTH following bisphosphonates**

- Anabolic effect still evident and strong if patient had been taking an antiresorptive before switching to PTH
  - Magnitude somewhat delayed and/or blunted compared to treatment-naïve pts
PTH and Alendronate (PaTH) Study

- 238 postmenopausal women with osteoporosis
  - Treatment naive
- Randomized to four treatment groups x 2 years
- Combination of PTH (1-84) + daily alendronate

<table>
<thead>
<tr>
<th>N</th>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>59</td>
<td>PTH(1–84)</td>
<td>PLB</td>
</tr>
<tr>
<td>60</td>
<td>PTH(1–84)</td>
<td>ALN</td>
</tr>
<tr>
<td>59</td>
<td>PTH(1–84) + ALN</td>
<td>ALN</td>
</tr>
<tr>
<td>60</td>
<td>ALN</td>
<td>ALN</td>
</tr>
</tbody>
</table>

Black, NEJM, 2003

Hypothesis: PTH + alendronate will increase BMD much more than either alone

**Changes in Trabecular Volumetric BMD by QCT (g/cm²)**

Concurrent use of PTH+ALN in PaTH: Summary

- No advantage of concurrent PTH + (daily) alendronate compared to monotherapy with PTH alone
- Anabolic effect of PTH, particularly on trabecular bone, is blunted by concurrent use of alendronate
Trial of once yearly zoledronic acid + teriparatide

- 360 patients
- Follow-up one year

Zoledronic acid

Cosman, J Bone Miner Res 2011

Changes in BMD at the hip

Changes in BMD at spine and hip

Changes in P1NP over 1 year: Alendronate vs. zoledronic acid

Black, NEJM 2003; Cosman, JBMR 2011
**Changes in P1NP over 1 year: Alendronate vs. zoledronic acid**

![Graph showing changes in P1NP over 1 year for PTH + ALN and PTH + ZOL](image)

- **Median Change P1NP (%)**
  - -100
  - 0
  - 100
  - 200
  - 300
  - 400

- **Month**
  - 0
  - 3
  - 6
  - 9
  - 12

- **Weeks**
  - 0
  - 4
  - 8
  - 12
  - 16
  - 20
  - 24
  - 28
  - 32
  - 36
  - 40
  - 44
  - 48
  - 52

- **Mean P1NP (ng/mL)**
  - 40
  - 80
  - 120
  - 160
  - 200

- **Legend**
  - PTH
  - PTH/BIS
  - BIS

- **Sources**
  - Black, NEJM 2003; Cosman, JBMR 2011

---

**Fractures (Only assessed as AEs)**

<table>
<thead>
<tr>
<th>Category</th>
<th>ZOL + TPTD n (%) (n=137)</th>
<th>TPTD alone n (%) (n=137)</th>
<th>ZOL alone n (%) (n=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical fractures (assessed as AEs only)</td>
<td>4 (2.9%)</td>
<td>8 (5.8%)</td>
<td>13 (9.5%)*</td>
</tr>
<tr>
<td>Spine fractures</td>
<td>0</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

* p=0.04 vs combination (post-hoc)

Cosman, J Bone Miner Res 2011

---

**PTH + Zoledronic acid**

- **BMD results similar to PTH+ALN in PaTH**
- **Pattern of marker changes is different**
  - Although not clear that it’s better
- **Fracture results intriguing**
  - But not an official study endpoint
- **Missing pieces:**
  - QCT vBMD (trabecular vs. cortical)
  - Adjudication of fractures
  - Longer-term follow-up
- **Denosumab similar to zoledronic acid with respect to rapid onset**

---

**Denosumab and Teriparatide trial (DATA)**

- **PTH(1–34)**
- **PTH(1–34) + DMAB**
- **DMAB**

- **100 patients**
- **Follow-up one year**

Tsai, Lancet 2013
Denosumab and Teriparatide trial (DATA)

- First combo to increase BMD more at spine and hip than either agent alone
- Why does DMAB seem to interfere less with formation than bisphosphonates?
  - Mechanism of action?
  - Frequency? (q 6 months)
- $$$ combo, but could be considered
  - Particularly if short-term (1-2 years)

Combination #3

- Use of antiresorptive after PTH
  - PaTH: 1 yr of PTH then 1 yr ALN or placebo

<table>
<thead>
<tr>
<th>N</th>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>59</td>
<td>PTH(1–84)</td>
<td>PLB</td>
</tr>
<tr>
<td>60</td>
<td>PTH(1–84)</td>
<td>ALN</td>
</tr>
<tr>
<td>58</td>
<td>PTH(1–84) + ALN</td>
<td>ALN</td>
</tr>
<tr>
<td>60</td>
<td>ALN</td>
<td>ALN</td>
</tr>
</tbody>
</table>

Change in spine BMD (DXA) over 24 months

- PTH discontinued
- 24 month change

Black, NEJM, 2005
What to do following PTH therapy?

- PTH followed by nothing will result in loss of most, if not all, BMD gains
- Bisphosphonates seem to add to BMD gains
- Follow PTH with some sort of antiresorptive therapy

Combination therapy with teriparatide: Conclusions

- Substantial literature about combination therapy, but no fracture outcomes
- Sequential antiresorptive then PTH: Still see increases in formation, BMD with PTH
  - May be slightly delayed/blunted
- If using PTH, probably best to use alone
  - Or with DMAB ($$$)
- PTH followed by antiresorptive seems to maximize BMD gains
Future of anabolic therapy

- Cyclic PTH? (e.g., 3- or 6-mo at a time?)
- Other forms of and delivery methods for PTH (e.g., PTHrP, transdermal PTH) in development
- Anabolics with other mechanisms of action
  - Anti-sclerostin Ab