Teriparatide Alone and in Combination with Antiresorptive Therapy

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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
  – Raloxifene
  – Estrogen
  – Calcitonin
  – Denosumab
- Anabolic agents
  – Teriparatide (injectable PTH)
Anabolic therapy *increases* bone remodeling rates

![Graph showing median change in bone formation and resorption markers over time.](image)

PaTH study, Black, et. al, NEJM, 2002

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) studied but not available in US
- Both require (currently) daily injection
  - Subcutaneous, abdomen

![Graph showing bone turnover markers over time.](image)

(adapted from Canalis et al., NEJM, 2007)

PTH increases bone formation markers before bone resorption markers

![Diagram of bone turnover markers.](image)

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 RM, et al. NEJM, 2001
Effect of PTH (1-34) on lumbar spine BMD

<table>
<thead>
<tr>
<th>Months</th>
<th>% Change (±SE)</th>
<th>Placebo</th>
<th>PTH 20 mcg</th>
<th>PTH 40 mcg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>~ 7%</td>
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<tr>
<td>2</td>
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<td>16</td>
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</tbody>
</table>

*** p < 0.001 vs. Placebo


Effect of PTH (1-34) on total hip BMD

<table>
<thead>
<tr>
<th>Months</th>
<th>% Change (±SE)</th>
<th>Placebo</th>
<th>PTH 20 mcg</th>
<th>PTH 40 mcg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>~ 2%</td>
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<td></td>
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<tr>
<td>6</td>
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<td>12</td>
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<td>18</td>
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<td>24</td>
<td>***</td>
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</tr>
</tbody>
</table>

*** p < 0.001 vs. Placebo


Effect of PTH (1-34) on risk of new vertebral fractures

-2 0 2 4 6 8 10 12 14

% of Women

<table>
<thead>
<tr>
<th>% of Women</th>
<th>No. of Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>64</td>
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<tr>
<td>2</td>
<td>22</td>
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<tr>
<td>4</td>
<td>2</td>
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<td>8</td>
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<td>10</td>
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<tr>
<td>12</td>
<td>2</td>
</tr>
</tbody>
</table>

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

* P < 0.001


PTH (1-34) and reduction in non-vertebral fragility fractures

20 mcg vs. placebo: RR=0.47 (0.25,0.88)

* p < 0.05 vs. Placebo

Histomorphometry:
PTH (1-34) in a 64 y.o. woman

Before
CTh: 0.32 mm
CD: 2.9 mm$^3$

After
CTh: 0.42 mm
CD: 4.6 mm$^3$

Dempster DW et al. J Bone Miner Res. 2001;16:1846-1853

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 antiresorpive therapy
  - Incident fx or active bone loss
- Glucocorticoid-induced osteoporosis

Combination PTH + antiresorption?

- PTH increases formation \textit{then} resorption
- Antiresorptives decrease resorption \textit{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
Combination PTH + antiresorptive?

3 distinct possibilities

1. Antiresorptives → PTH
2. Antiresorptives + PTH
3. PTH → Antiresorptives

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

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

**Changes in Trabecular Volumetric BMD by QCT (g/cm³)**

**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

**Changes in total hip and femoral neck BMD**

Weeks

- Total Hip BMD
- Femoral Neck BMD

**Changes in P1NP over 1 year: Zoledronic acid vs. alendronate**

**Fractures (assessed as AEs only)**

<table>
<thead>
<tr>
<th>Category</th>
<th>ZOL + TPTD n (%)</th>
<th>TPTD alone n (%)</th>
<th>ZOL alone n (%)</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)
**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

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**Denosumab and Teriparatide trial (DATA)**

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

- 100 patients
- Follow-up one year

Tsai, Lancet, 2013

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**Denosumab and Teriparatide trial (DATA)**

T sai, et al., Lancet, 2013

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**PTH + Denosumab**

- 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>
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<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>


**Change in spine BMD (DXA) over 24 months**

- PTH discontinued
  - PTH (1–84) +12%
  - PLB + 4%
  - ALN + 8%

- ALN only, 24 months

**Change in trabecular spine BMD (QCT) over 24 months**

- PTH discontinued
  - PTH (1–84) +30%
  - PLB +13%

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
Cyclic PTH:
PTH – Ibandronate – PTH - Ibandronate

Schafer et al, J Clin Endocrinol Metab 2012

Bone Formation Increases with a Second Course of PTH(1-84)

 Sequential

Schafer et al, J Clin Endocrinol Metab 2012
**PTH (1-34) dosing**

- 40 mcg more effective on BMD
- 20 and 40 mcg similar fracture reduction
- More side effects (e.g. nausea, dizziness) with 40 mcg dose
- 20 mcg approved

**Impact of PTH + bisphosphonate on bone formation (the PaTH study)**

![Graph showing the impact of PTH (1–84) and ALN on bone formation and resorption.](image)

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

- Month: 0 3 6 9 12

**The Holy Grail for combination therapy**

![Graph showing the comparison between bone formation and resorption with PTH (1-34) and ALN.](image)

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

- Month: 0 3 6 9 12

**PTH (1–34) added to ongoing alendronate: lumbar spine BMD**

- Daily PTH (1–34)+ALN
- ALN only

![Graph showing % change in lumbar spine BMD](image)


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**Changes in serum CTX and P1NP**

- Mean Serum β-CTX (ng/mL)
- Mean Serum PINP (ng/mL)

![Graph showing serum CTX and PINP](image)

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**Finite element modeling of femoral strength in PaTH**

![Graph showing change in femoral strength from baseline](image)

*Keaveny et al. JBMR 2008*

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**Trial of once yearly zoledronic acid + teriparatide**

- Daily PTH (1–34)+ALN
- ALN only

![Graph showing changes in serum CTX and P1NP](image)

*Cosman, et al. J Bone Miner Res 2011*
PTH increases bone formation markers before bone resorption markers