PTH and PTH Combination therapy for osteoporosis

Dennis Black, PhD
Dept. of Epi. and Biostat
UCSF

Disclosures
D. Black
Research Funding: Novartis, Merck
Consulting: Amgen, Lilly, Zosano, Nycomed

Outline
- Overview of anabolic therapy
- Combining anabolic and antiresorptive therapies
  (note: will skip some slides in syllabus)

Anabolic therapy increases bone remodeling rates

* PaTH study, Black, et. al, NEJM, 2002
Background: 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 @ 100 mcg/day (not available in US)
  - Other fragments in development
- All require (currently) daily injection

PTH (1-34) (Teriparatide)
Fracture Prevention Trial

- 1637 PM women
- Randomized to PBO, rPTH(1-34) 20 ug or 40 ug
- Fractures primary endpoints
- 3 year study, halted after 21 mos (median)
  - Safety problem with high doses in rodents
- Teriparatide, only anabolic in US


Effect of PTH 1-34 on Lumbar Spine BMD

<table>
<thead>
<tr>
<th>% Change (±SE)</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH 20 mcg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>***</td>
<td>***</td>
<td></td>
</tr>
<tr>
<td>PTH 40 mcg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>***</td>
<td>***</td>
<td>***</td>
<td>***</td>
<td></td>
</tr>
</tbody>
</table>

~ 7%

*** p < 0.001 vs. Placebo


Effect of PTH 1-34 on Total Hip BMD

<table>
<thead>
<tr>
<th>% Change (±SE)</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH 20 mcg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH 40 mcg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>***</td>
<td>***</td>
<td>***</td>
<td>***</td>
<td></td>
</tr>
</tbody>
</table>

~ 2%

*** p < 0.001 vs. Placebo

**Effect of rhPTH(1-34) on The Risk of New Vertebral Fractures**

- **Placebo** (n=448): 64
- **rhPTH 20mg (n=444)**: 22

No. of women who had > 1 fracture

<table>
<thead>
<tr>
<th>% of Women</th>
<th>Placebo (n=448)</th>
<th>rhPTH 20mg (n=444)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>64</td>
<td>22</td>
</tr>
</tbody>
</table>

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

*P < 0.001


**Histomorphometry-- Effect of PTH 1-34 in a 64-Year-Old Woman**

**Before**
- CtTh: 0.32 mm
- CD: 2.9 mm³

**After**
- CtTh: 0.42 mm
- CD: 4.6 mm³


**Dose of PTH (1-34) (teriparatide)**

- 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

**PTH 1-34 and reduction in Non-vertebral Fragility Fracture**

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

*P < 0.05 vs. Placebo

**PTH as clinical treatment for osteoporosis**

- PTH very effective in increasing BMD and decreasing bone strength
- Approved for up to 2 years duration
- Limited adoption in clinical practice
  - Cost (~$10,000-14,000/year)
  - Need for daily injections
- New molecules (different fragments), delivery modes under development
- May become more widely used
  - Shorter courses of therapy
  - In combination with antiresorptive

**Clinical question: Combination of PTH with antiresorptives?**

- 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

**Impact of PTH vs. bisphosphonates on bone formation (PaTH) study**

![Graph showing the impact of PTH vs. bisphosphonates on bone formation (PaTH) study.](image)


**The Holy Grail for Combination therapy**

![Graph showing the Holy Grail for Combination therapy.](image)
Clinical question: combination of PTH with antiresorptives?

- 3 distinct possibilities

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

- Focus on recent RCT’s, primarily with bisphosphonates

PTH Combination #1

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

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

- Anabolic effect still evident and strong
  - Magnitude somewhat delayed and/or blunted compared to treatment naïve patients
  - May be similar whether or not antiresorptive is continued

**PTH combination # 2**

- Concurrent initiation of PTH and antiresorptives (treatment-naive women)
- PaTH year 1*:
  - PTH vs PTH & ALN
  - PTH vs PTH & Zoledronic acid
  - PTh vs. PTH & denosumab (Lancet, 5/13)


**Antiresorptives + PTH**

**PTH and Alendronate (PaTH) study:**

- 238 post-menopausal women with osteoporosis
  - Treatment naive
- Randomized to four treatment groups for 2 years
- Combination of PTH 1-84 and 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>


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

- Synergistic effect
- Additive effect

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

**Spine**

- Mean Change (%)
- PTH: 30
- PTH/ALN: 40
- ALN: 20

**Total Hip**

- Mean Change (%)
- PTH: 20
- PTH/ALN: 30
- ALN: 10

*p<.01

NEJM 2003
Zoledronic acid (annual) and Teriparatide trial

- 360 patients
- Follow-up one year
- LS spine BMD main outcome
- Hypothesis: Zoledronic acid will not blunt effects of PTH

Cosman, ref??

Denosumab and Teriparatide trial (DATA)

- 100 patients
- Follow-up one year
- LS spine BMD main outcome
- Hypothesis: More BMD increase with combination then either alone

Tsai, et al. Lancet, 5/13

Effect of teriparatide vs. denosumab alone and in combination on spine and hip BMD

Combination of D’mab and teriparatide

- First combination study where two together increased BMD more at both hip and spine than either alone. Promising results.
- Why D-mab seems to interfere less with formation than bisphosphonates?
  - Frequency? Mechanism of action?
  - Definitely worth more study
- Pricy combination but could be effective, perhaps for short period (1-2 years)

Tsai, et al. Lancet, 5/15/13
**Concurrent initiation of PTH with antiresorptives from PaTH: summary**

- No advantage to concurrent use of PTH with (daily) alendronate compared to monotherapy with PTH alone.
- Anabolic effect of PTH, particularly on trabecular bone, is blunted by concurrent use with alendronate.

**Combination studies #3**

- Use of antiresorptives following PTH.
- PaTH: 1 year of PTH followed by 1 year of 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>39</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 DXA spine BMD over 24 months**

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


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

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

Finite element modeling of femoral strength in PaTH

What to do following PTH treatment?

- PTH followed by nothing will result in the loss of most, if not all, gains
- Bisphosphonates seem to add to BMD gains
- Clinical conclusion: Follow PTH with some form of antiresorptive therapy
- Many interesting future BMD studies

Some Limitations on what we know about PTH combination

- BMD/Marker studies only: no fracture data
- Most of studies with alendronate
  - Other bisphosphonates and other a/r’s may differ
- ...

Combination of PTH Therapy with Antiresorptives: Conclusions

- Rapidly growing literature of BMD (not fracture) trials
- After antiresorptive therapy, still see increases in bone formation and BMD
  - Maybe be slightly delayed/blunted
- PTH therapy followed by anti-resorptives seems to maximize BMD gains
- When PTH initiated, probably best alone
- More studies (particularly of other A-R’s) needed (some in progress)