**PTH and PTH Combination therapy for osteoporosis**

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**Anabolic therapy increases bone remodeling rates**

 Median Change (%)  
-100 0 100 200 300 400  
Month 0 3 6 9 12  
Formation (P1NP)  
Resorption (CTX)  
PTH  
ALN  

**Background: Types of 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
- Response is very dose-dependent
- All require (currently) daily injection

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

**Disclosures**

D. Black
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Consulting: Nycomed
**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


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**Effect of PTH 1-34 on Lumbar Spine BMD**

- % Change (±SE)
- Months
- ***** p < 0.001 vs. Placebo
- ~ 7%

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**Effect of PTH 1-34 on Total Hip BMD**

- % Change (±SE)
- Months
- ***** p < 0.001 vs. Placebo
- ~ 2%

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

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

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


<table>
<thead>
<tr>
<th>Days since randomization</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>PTH 40 *</td>
</tr>
<tr>
<td></td>
<td>PTH 20 *</td>
</tr>
</tbody>
</table>

* p < 0.05 vs. Placebo

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

**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 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 (~$7000/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

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

<table>
<thead>
<tr>
<th>Month</th>
<th>PTH(1–84)</th>
<th>ALN</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-100</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>9</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>12</td>
<td>400</td>
<td>400</td>
</tr>
</tbody>
</table>

**Bone Formation (P1NP)**

**Resorption (CTX)**


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**Effect of PTH 1-34 (40mcg) on spine BMD by DXA in women taking estrogen + progestin**

<table>
<thead>
<tr>
<th>Months</th>
<th>% Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>24</td>
<td>20</td>
</tr>
</tbody>
</table>

*Mean ± SE p<.0001

Roe, Arnaud 1999
Clinical question: combination of PTH (1–84) with antiresorptives?

- 3 distinct possibilities

- **Antiresorptives** → **PTH**
- **Antiresorptives** → **PTH**
- **Antiresorptives + PTH** → **Antiresorptives**

**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)**

![Graph showing % change in lumbar spine BMD over time for different treatment groups.]


**3 month on-off cycles of PTH(1-34): Lumbar Spine BMD**

![Graph showing lumbar spine BMD over time for different treatment groups.]

* *p<0.05 Change from Baseline ALN Only vs both PTH groups*
**PTH following bisphosphonates**

Several additional studies in 2006-07

Similar conclusions:

- Anabolic effect still evident and strong
  
  Magnitude somewhat blunted compared to treatment naïve patients

  May be similar whether or not antiresorptive is continued

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**PTH combination # 2**

- Concurrent initiation of PTH and antiresorptives (treatment-naïve women)
- PaTH year 1*:
  - PTH vs PTH & ALN

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**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)

<table>
<thead>
<tr>
<th>Spine</th>
<th>Total Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH</td>
<td>PTH/ALN</td>
</tr>
</tbody>
</table>

** p<.01

NEJM 2003

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

To be studied:
- Does less frequent or less potent antiresorptive work better with PTH?

Combination studies #3

- Use of antiresorptives following PTH
- PaTH: 1 year of PTH followed by 1 year of ALN or placebo


Change in DXA spine BMD over 24 months

Mean Change (%)

<table>
<thead>
<tr>
<th>Month</th>
<th>PTH (1–84)</th>
<th>PLB</th>
<th>ALN</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>+12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>+4%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Change in DXA spine BMD over 24 months of treatment**

- **Mean change (%)**
  - 0 0
  - 5 5
  - 10 10
  - 15 15
  - 20 20

- **Month**
  - 0
  - 12
  - 24

**PLB**
- PTH discontinued
- PLB

**ALN**
- PTH (1–84)
- ALN + 12%
- ALN + 8%

**24 month change**
- +12%
- +4%


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

- **Mean change (%)**
  - 0
  - 8
  - 16
  - 24
  - 32
  - 40

- **Month**
  - 0
  - 12
  - 24

**PLB**
- PTH discontinued
- PLB

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

**24 month change**
- +30%
- +13%


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

- **Mean ± 95% CI**
  - *P<0.05 within group from baseline

- **TREATMENT**
  - YR1—YR2
  - PTH-PLB
  - PTH-ALN
  - OMB-ALN
  - ALN-ALN

- **CHANGE IN FEMORAL STRENGTH FROM BASELINE (%)**

- **YEAR 1**
  - *P<0.05
  - *P<0.01

- **YEAR 2**
  - *P<0.05

*Keaveny et al. JBMP, 2008*

**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
- Most studies with daily bisphosphonates
  - Weekly, monthly, yearly may be different
  - New study with once per year ZOL was similar

Combination of PTH Therapy with Antiresorptives: Conclusions:

- Rapidly growing literature of BMD (not fracture) trials
- In patients on antiresorptive therapy, increases in bone formation and BMD with PTH after A-R’s
  - Some blunting of response to PTH depending on type of previous A-R
- 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)

Future of Anabolic Therapy:

- Teriparatide (PTH(1-34)) will soon be off patent
  - Might be more widely used at lower cost
- Other forms and delivery methods being developed (oral, nasal, patch) but not clear that any will succeed
- Other anabolic therapies being studied (not PTH or analogues)...Steve Cummings to discuss