**PTH and PTH Combination therapy for osteoporosis**

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**Disclosures D. Black**

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**Anabolic therapy increases bone remodeling rates**

- Median Change (%)
- Resorption (CTX) vs. Formation (P1NP)
- PTH and ALN in Treatment Groups
- PaTH study, Black, et al, NEJM, 2002

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**For patients taking bisphosphonates who want to start PTH(1-34)..**

1. They should expect no anabolic response
2. They should wait at least 6 months before starting
3. There is a strong anabolic response but it is somewhat delayed and blunted compared to treatment naïve patients
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

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>Months</th>
<th>% Change (±SE)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>~ 7%</td>
</tr>
<tr>
<td>6</td>
<td>***</td>
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<tr>
<td>12</td>
<td>***</td>
</tr>
<tr>
<td>18</td>
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*** p < 0.001 vs. Placebo


Effect of PTH 1-34 on Total Hip BMD

<table>
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<th>% Change (±SE)</th>
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*** p < 0.001 vs. Placebo

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

<table>
<thead>
<tr>
<th>No. of women who had ≥ 1 fracture</th>
<th>Placebo (n=448)</th>
<th>rhPTH 20mg (n=444)</th>
</tr>
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<tbody>
<tr>
<td>% of Women</td>
<td>64</td>
<td>22</td>
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</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 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

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


**The Holy Grail for Combination therapy**
Effect of PTH 1-34 (40mcg) on spine BMD by DXA in women taking estrogen + progestin

Clinical question: combination of PTH with antiresorptives?

- 3 distinct possibilities

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)

**PTH following bisphosphonates**

Several additional studies since 2007  
Similar conclusions:  
- Anabolic effect still evident and strong  
  - Magnitude somewhat delayed and/or blunted compared to treatment naive patients  
  - May be similar whether or not antiresorptive is continued

**PTH combination # 2**

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

**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

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

- Synergistic effect
- Additive effect

Changes in Trabecular Volumetric BMD by QCT (g/cm$^3$)

** p<.01

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

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Change in DXA spine BMD over 24 months

Change in DXA spine BMD over 24 months of treatment

Mean change (%)

Month

PLB

ALN

PTH (1–84)

24 month change

+12%

+4%

+8%

PLB

ALN

PTH discontinued


Change in QCT trabecular spine BMD over 24 months

Mean change (%)

Month

PLB

ALN

PTH (1–84)

24 month change

+30%

+13%

+8%


Finite element modeling of femoral strength in PaTH

TREATMENT

YR1—YR2

CHANGE IN FEMORAL STRENGTH FROM BASELINE (%)

Mean ± 95% CI

YEAR 1

YEAR 2

Keaveny et al. JBMR, 2008

* P<0.05 within group from baseline

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)

Future of Anabolic Therapy

- Other forms and delivery methods for PTH being developed (oral, nasal, patch) but not clear that any will succeed
- Other types of anabolic therapies being studied (not PTH or analogues)…