Anabolic Therapy and in Combination with Antiresorptives

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Outline

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

Treatment of Osteoporosis

• Antiresorptive agents
  – Bisphosphonates
  – Denosumab
  – Raloxifene and estrogen
• Anabolic agents
  – Teriparatide (injectable PTH)
  – Others in development
Parathyroid Hormone (PTH)

- 84 amino acid sequence
- Most of bone activity in first 34 amino acids
  - PTH (1-34) (teriparatide) approved @ 20 mcg/day
- Requires (currently) daily injection
  - Patches and other forms being investigated

Anabolics and antiresorptives have opposite effects on bone remodeling

1637 postmenopausal women
Randomized to placebo, PTH (1-34) 20 ug, or PTH (1-34) 40 ug
Fracture was primary endpoint
3-year study planned, 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

*** p < 0.001 vs. Placebo
Effect of PTH (1-34) on total hip BMD


*** p < 0.001 vs. Placebo

Effect of Teriparatide (20 ug) on risk of new vertebral fractures

Teriparatide and reduction in non-vertebral fragility fractures


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

Teriparatide in clinical practice

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

- 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

Combination PTH + antiresorptive?

3 distinct possibilities

1. Antiresorptives → PTH
2. Antiresorptives + PTH
3. PTH → Antiresorptives
Pre-treatment with antiresorptives followed by PTH

- Key clinical question
- Many patients on bisphosphonates and other antiresorptives

Summary:

**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-naive pts
Combination #2

Concurrent initiation of PTH plus antiresorptive in treatment naïve women

- PTH+alendronate
- PTH+zoledronic acid
- PTH+dénosumab

Antiresorptives + PTH

Year 1

- PTH(1–84)
- ALN

Year 2

- PTH(1–84)
- ALN
- PTH(1–84) + ALN
- ALN


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

Synergistic effect

Additive effect

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

**p<.01**

**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

**What about teriparatide with other antiresorptives?**

- **TPTD with IV ZOL (1 year trial, BMD trial)**
  - BMD effects similar to combination with alendronate (PaTH)
- **TPTD with denosumab (1 year BMD trial)**
  - Larger increases in BMD than with combination with alendronate
  - Very expensive, no fracture data
- More details in “bonus slides”

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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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</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>


Change in spine BMD (DXA) over 24 months

Mean Change (%)

PTH discontinued

24 month change

Change in spine BMD (DXA) over 24 months


Change in trabecular spine BMD (QCT) over 24 months

What to do following PTH therapy?

• PTH followed by nothing will result in loss of most, if not all, BMD gains
• Bisphosphonates add to BMD gains
• In general for clinical use: Follow PTH with some sort of antiresorptive therapy

Combination therapy with teriparatide: Summary

• 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
• Concurrent use:
  - If using PTH, probably best to use alone
  – Or with DMAB ($$$)
• PTH followed by antiresorptive will maximize/maintain BMD gains
Future of anabolic therapy (hear)

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

Trial of once yearly zoledronic acid + teriparatide

- PTH(1–34)
- PTH(1–34) + Zol.
- Zoledronic acid

- 360 patients
- Follow-up one year

Changes in total hip and femoral neck BMD

<table>
<thead>
<tr>
<th></th>
<th>Total Hip BMD</th>
<th>Femoral Neck BMD</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean % Change in BMD</td>
<td>Mean % Change in BMD</td>
</tr>
<tr>
<td>ZOL+ TPTD</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>TPTD alone</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>ZOL alone</td>
<td>*</td>
<td>*</td>
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</tbody>
</table>

*P<0.05 vs TPTD alone
†P<0.05 vs ZOL alone

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

<table>
<thead>
<tr>
<th></th>
<th>PTH + ZOL</th>
<th>PTH + ALN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean PINP (ng/mL)</td>
<td>Median Change P1NP (%)</td>
</tr>
<tr>
<td>PTH</td>
<td>PTH/BIS</td>
<td>BIS</td>
</tr>
</tbody>
</table>

Black, NEJM 2003; Cosman, JBMR 2011
Fractures (assessed as AEs only)

<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)

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)

- 100 patients
- Follow-up one year

Tsai, Lancet, 2013

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Denosumab and Teriparatide trial (DATA)

Tsai, et al., Lancet, 2013
• 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)

Cyclic PTH:
PTH – Ibandronate – PTH - Ibandronate

Schafer et al, J Clin Endocrinol Metab 2012
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
Anabolics and antiresorptives have opposite effects on bone remodeling


The Holy Grail for combination therapy
Finite element modeling of femoral strength in PaTH

* $p<0.05$ within group from baseline

Keaveny et al. JBMR 2008