Hot Topics in Bone Disease in 2017: Building Better Bones – Breaking News in Osteoporosis

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Disclosures

• **Industry support**
  • None

• **Off label drug use**
  • None
Objectives

At the end of the presentation, the attendee will have reviewed:

• Discuss the use of anabolic (teriparatide) therapy in orthopedic spinal fusion surgery

• Assess the efficacy of anabolic (teriparatide) therapy on fracture healing, to include atypical femoral fractures
Teriparatide Therapy and Qualitative Improvement in Bone Micro-architecture

Paired iliac crest bone biopsies (same magnification shown) in a 64 y.o. woman pre- and post- teriparatide therapy. Increase in cortical thickness (320 to 420 μm) and connectivity density (2.9 to 4.6 per mm³).

Teriparatide Therapy and Qualitative Improvement in Bone Micro-architecture

Mean age men 49 yrs and women 54 yrs (postmenopausal, taking HRT) with paired iliac crest bone biopsies pre- and post- rhPTH*

<table>
<thead>
<tr>
<th></th>
<th>Men (n=8)</th>
<th></th>
<th>Women (n=8)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>18 mos</td>
<td>Before</td>
<td>36 mos</td>
</tr>
<tr>
<td>Cancellous bone volume (%)</td>
<td>22.54</td>
<td>±2.47</td>
<td>26.03</td>
<td>±0.74</td>
</tr>
<tr>
<td></td>
<td>21.28</td>
<td>±3.52</td>
<td>22.39</td>
<td>±3.09</td>
</tr>
<tr>
<td>Trabecular number (per mm)</td>
<td>1.25</td>
<td>±0.06</td>
<td>1.33</td>
<td>±0.06</td>
</tr>
<tr>
<td></td>
<td>1.33</td>
<td>±0.10</td>
<td>1.31</td>
<td>±0.13</td>
</tr>
<tr>
<td>Trabecular separation (μm)</td>
<td>763</td>
<td>±39</td>
<td>713</td>
<td>±34</td>
</tr>
<tr>
<td></td>
<td>731</td>
<td>±57</td>
<td>748</td>
<td>±73</td>
</tr>
<tr>
<td>Trabecular thickness (μm)</td>
<td>196</td>
<td>±15</td>
<td>208</td>
<td>±9</td>
</tr>
<tr>
<td></td>
<td>179</td>
<td>±9</td>
<td>197</td>
<td>±13</td>
</tr>
<tr>
<td>Connectivity density (per mm)</td>
<td>3.6</td>
<td>±0.39</td>
<td>4.35</td>
<td>±0.37</td>
</tr>
<tr>
<td></td>
<td>3.28</td>
<td>±0.69</td>
<td>4.64</td>
<td>±0.81</td>
</tr>
<tr>
<td>Cortical thickness (μm)</td>
<td>612</td>
<td>±60</td>
<td>643</td>
<td>±37</td>
</tr>
<tr>
<td></td>
<td>420</td>
<td>±104</td>
<td>771</td>
<td>±113</td>
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Impaired healing in 5-10% of fractures\(^1\)

Teriparatide effect on fracture healing

- **Femoral neck**
  - Placebo controlled DBRCT (161 patients)\(^2\)
  - **Outcome**: ns in rate of fracture healing at 12 mos

- **Radial**
  - Placebo controlled DBRCT (102 PM women)\(^3\)
  - **Outcome**: ns with 40 μg/d, but shorter time to cortical bridging in the 20 μg/d group (p=0.006)

- **Intertrochanteric**
  - Active controlled DBRCT (71 M/F) – ns change\(^4\)
  - Retrospective cohort study (n=73) with shorter mean union time in unstable fractures\(^5\)

Objective – 1
Effect of teriparatide in orthopedic spine surgery

• **Bone fusion rate** after instrumented lumbar posterolateral fusion was higher with teriparatide vs risedronate (p<0.05) in PMO  (Spine 2012;37(23):E1464)

• **Bone fusion rate** and average **bone union duration** higher in the teriparatide long-duration vs short-duration group (p<0.05) in PMO  (Asian Spine J 2015;9(4):573)

• **Pedicle screw loosening** after posterolateral fusion was significantly reduced with teriparatide vs risedronate (p<0.05) in PM women  (Spine 2013;38(8):E487)

• **Mean insertional torque** value was significantly higher with pre-operative teriparatide vs controls (p<0.01) in fusion surgery using pedicle screws  (J Neurosurg Spine 2014;21(3):425)
Teriparatide (TPT) and Spine Surgery
Effect on bone fusion

• **Study-1**: 57 women, 77 (± 7) yrs old with PMO*
  - Decompression / posterolateral fusion + bone graft
  - RIS 17.5 mg/wk (n=28) vs TPT 20 μg/day (n=29)

• **Outcomes**: 1 year
  - **Pain** scores improved postop – ns between groups
  - **Bone union rate** – assessed by CT imaging
    - 82% TPT vs 68% RIS group (p<0.05%)
    - Ave duration of bone union was 8 mos with TPT vs 10 mos in RIS group

Teriparatide (TPT) and Spine Surgery  
Effect on bone fusion

• **Study-2:** 45 women, 71 (± 7) yrs old with PMO*
  - Decompression / posterolateral fusion + bone graft
  - RIS 17.5 mg/wk (13 mos) vs TPT 20 μg/day

• **Outcomes:** short (5.5 mos) vs long (13 mos) TPT
  - **Bone union rate** and ave **duration** for bone union
    - 92% and 7.5 mos with long-duration TPT
    - 80% and 8.5 mos with short-duration TPT
    - 70% and 10 mos with RIS therapy
  - Both TPT groups superior to RIS (p<0.05)
  - Longer (vs shorter) TPT therapy superior (p<0.05)

Teriparatide (TPT) and Spine Surgery Pedicle screw (PS) loosening

• **Study:** 62 women, 71 (± 7) yrs old with PMO*  
  - Decompression / posterolateral fusion + bone graft  
  - 3 groups: RIS 2.5 mg/d, TPT 20 μg/day, controls

• **Outcomes:** 1-year evaluation by CT scans  
  - **PS loosening**  
    - 7–13% with TPT  
    - 13–26% with RIS  
    - 15–25% in controls  
    - PS loosening with TPT group lower than RIS and control groups (p<0.05). RIS ns from controls.

Teriparatide (TPT) and Spine Surgery
Pedicle screw (PS) insertional torque

- **Study:** 29 women, mean 72 yrs with PMO*
  - Thoracic or lumbar fusion + bone graft
  - TPT (n=13) 20 μg/day or 56.5 μg once/wk, vs controls (n=16)
    - Pre-op TPT: mean 61.4 days, minimum 31 days

- **Outcomes:** insertional torque value¹
  - Mean insertional torque value with TPT group (1.28 Nm) higher vs controls (1.08 Nm), p<0.01
  - Negligible correlation between insertional torque and duration of preoperative TPT, and between daily vs weekly TPT (p=0.07)

¹Insertional torque value obtained when screw shank completely anchored to the entrance point.

*BMD ns between groups. PMO, postmenopausal osteoporosis.
Teriparatide (TPT) and Spine Surgery
Pedicle screw (PS) insertional torque values

**Insertional torque stratified by length.** Controls; ns difference. TPT group with greater insertional torque vs controls for both screw lengths (*p<0.05; **p<0.01).

**Insertional torque for 3 screw diameters.** In both control and TPT groups, larger diameter screws had greater insertional torque. TPT difference seen for the largest diameter category (*p<0.01).

¹Insertional torque value obtained when screw shank completely anchored to the entrance point.
Objective – 2
Assess efficacy of teriparatide on AFF healing

**Microarchitecture** (Bone 2013;52:360)
- ↓ in cortical bone mineralization density (HRpQCT)
- ↑ mean CTX (196%, p=0.057) & P1NP (343%, p=0.01)
- Fracture healing on bone scans

**Bone histomorphometry** (Semin Arthritis Rheum 2015;44:477)
- ↑ in bone formation, mineralizing surface, and mineral apposition within 6 mos

**Fracture healing** (Case studies)
- Healing of non-union fractures (radiographs)
- Resolution of pain
Atypical Femur Fractures (AFF)

- **Rare;** ~1% of all femoral fractures
  - However, risk appears to ↑ with increased duration of anti-resorptive drug exposure¹ ²
  - Clinical and radiographic features distinguish them from typical OP fractures

Atypical Femoral Fractures
Criteria for diagnosis*

Pre-op: oblique and transverse fractures (*white arrows*) and medial “spike” (*black arrow*).
Post-op: focal cortical thickening with “beaked” appearance (*arrow*)

**Major features***
- Minimal or no trauma
- Transverse or oblique Fx (distal to lesser trochanter and proximal to the supracondylar flare)
- Non-comminuted Fx
- Complete Fx through both cortices, ± medial spike
- Incomplete Fx involves only the lateral cortex

**Minor features***
- Use of bisphosphonate Rx >3 yrs, PPI’s, and steroids
- Associated RA and ↓vit-D
- Prodrome pain in >50%
- Local periosteal reaction
- Bilateral Fx’s
- Delayed healing

Subtrochanteric Femur Fractures
National observational register based studies

• **Studies:** cross-sectional (n=11,944) and matched cohort study (n=5,187; controls=10,374) with hip Fx’s
  • 7% of typical hip Fx’s and 7% atypical femur Fx’s were both exposed to ALN
  • Same HR for hip (1.45) & atypical femur Fx’s (1.46)
  • Identical ratio of typical / atypical hip Fx’s in ALN and control cohorts, even with long-term ALN Rx

• **Mechanism unknown**
  • Severely suppressed bone turnover?
  • Normal subset of femur fractures?

HR, hazard ratio; Fx, fracture; ALN, alendronate; Rx, therapy.
Suppression of Bone Turnover

Bone “remodeling” activity

Physiologic Remodeling

Normal Bone

Remodeling Too Low
OM: under-mineralized
ART: over-mineralized?

Remodeling Too High
↓ Bone mass/structure
↑ Stress risers

ART, anti-resorptive therapy. OM, osteomalacia.
Teriparatide and AFF
Effect on bone remodeling

• **Prospective study:** 14 consecutive patients presenting with AFF offered teriparatide Rx
  
  • **AFF:** 6 complete and 8 incomplete fractures
    • BisP use 4 to 10 yrs (n; ALN=11, RIS=1, APD/ZOL=2)
  
  • **HRpQCT:** high resolution peripheral micro-computed tomography of distal radius and distal tibia analyzed cortical BMD
    • Baseline and 6 mos, compared to controls
  
  • **Teriparatide:** 6 mos TPT at 20 μ/day s.q. (n=5)
    • Mean duration BisP use 8 yrs (vs 6 yrs for non-TPT use)
    • 4 persistent non-union/pain; 1 completion of stress Fx

Teriparatide and AFF
Effect on bone remodeling

• Results
  • Cortical density – HRpQCT
    • Mean cortical bone mineralization density decreased (vs no shift in 5 healthy age/gender matched controls)
  • Bone BCM
    • Baseline mean CTX (191 ng/L) increased 196%, p=0.057
    • Baseline mean P1NP (21 mcg/L) increased 343%, p=0.01

BCM, biochemical markers. CTX, C-telopeptide. P1NP, procollagen type 1 N-terminal propeptide.
The attenuation value of fully mineralized bone is assigned a value of 100%, and remaining voxels classified relative to this value: **white** 0%, (void; having attenuation as background); **blue**: 1–50%; **green** 51–70%; **yellow** 71–95%; **red**: >95% of maximum value. Changes in the distribution of voxels are captured by the left shift in the **void bone matrix distribution curve**. After 6 mos of treatment, more of the total voxels contain bone of lower density; voxels of higher density (yellow in rectangle a) became less dense (green in rectangle b and e). **Reduction in density of a given voxel may be due to replacement of mineralized bone matrix by new, less densely mineralized bone matrix** (higher quality?).
HRpQCT Distal Radius – pre/post PTH

Bone scintigraphy scans pre- and 6 mos post- teriparatide treatment. Reduction in the intensity of isotope uptake (n=4). One patient refused a repeat scan as she had fracture union and was pain free.

Teriparatide and AFF
Effect on bone remodeling – bone biopsy data

• **Study:** quantitative bone histomorphometry performed pre and post- teriparatide Rx in 15 patients with AFF
  - Mean BisP duration 7 yrs (range 6-11 yrs)
  - Intramedullary rods in all (6 wks to 7 mos prior)

• **Pre-treatment**
  - Bone formation, mineralizing surface, and mineral apposition unmeasurable in 7 and below ave in 8
  - Baseline BCM & histomorphometry – no correlation*

• **Post-treatment** (6 mos. teriparatide, 20 μg/day s.q.)
  - Bone formation, mineralizing surface, and mineral apposition all increased with teriparatide Rx

*Four patients with the highest urinary NTX and BSAP had the lowest bone dynamic parameters; also, BCM change inconsistent after Rx. Miller PD, et al. Semin Arthritis Rheum 2015;44(5):477.*
AFF and Teriparatide Therapy
Iliac crest bone biopsy

Pre-teriparatide baseline features of cancellous bone. Case: (1) No evidence of osteoclastic / osteoblastic activity. No osteoid is present. (2) The total osteoid surface not measurable.

Effect of 6 mos. teriparatide treatment on cancellous bone. Case: (1) Several trabeculae partially covered with osteoid, indicating functional osteoblastic activity. (2) The total osteoid surface was 11%.

## Teriparatide Therapy for AFF – Fracture Outcomes (Case reports)

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<tr>
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<th>Ref-1</th>
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<th>Ref-3</th>
<th>Ref-4</th>
<th>Ref-5</th>
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</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td>PMO. ALN 13 yrs.</td>
<td>PMO. ALN 13 yrs.</td>
<td>PMO. ALN 4 and 6 yrs.</td>
<td>PMO. ALN 12 yrs. + IBN 1 yr.</td>
<td>PMO. ALN 4 yrs.</td>
</tr>
<tr>
<td><strong>Fx Issue</strong></td>
<td>Bilateral incomplete AFF (MRI + stress Fx’s).</td>
<td>Left AFF. Right femur lytic lesion.</td>
<td>Incomplete AFF’s in 2 patients.</td>
<td>Left AFF. Incomplete right AFF 11 mos after Rx.</td>
<td>Right AFF</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>25(OH)D low; 50,000/wk Rx did not alter pain, then added teriparatide for 12 mos.</td>
<td>Surgical left femur locked intramedular nail, plus teriparatide for 12 mos.</td>
<td>Surgical locking plates, plus teriparatide for 12 mos.</td>
<td>Surgical intramedular nail, plus teriparatide for 24 mos.</td>
<td>Surgical intramedular nail, plus RIS for 1 yr, then teriparatide for non-healing</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Cortical bone bridging at 6 mos. At 1-yr, BMD L-sp ↑ 1.9% but hip ↓ 4%. At 16 mos, no pain. Fx healing Complete.</td>
<td>Pain resolved in right hip.</td>
<td>Patients w/o pain at 2 &amp; 3 wks after surgery.</td>
<td>BMD ↑ both at the L-sp and hip. Left-hip healed at 4 mos Rx.</td>
<td>Serum levels C-telopeptide ↑ 22% and osteocalcin ↑ 300% at 3 mos.</td>
</tr>
<tr>
<td></td>
<td>Lytic lesion in right hip healed.</td>
<td>Fx’s almost healed at 3 &amp; 6 mos in 2 patients.</td>
<td>Right hip pain &amp; Fx found at 11 mos Rx; healed at 24 mos Rx.</td>
<td>Fx closure at 1 mos.</td>
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Sequential PMO Therapy
Switch regimen to alternative drug

• Alternate drug treatment after ALN or RIS
  • **PubMed search**, from 11 studies prospectively assessing treatment after ALN or RIS in PMO
    • No study had power to assess Fx efficacy
    • All studies < 24 mos duration

• **BMD outcomes**
  • BMD *maintained* with ALN switch to → RAL, RIS, IBN, or ZOL*
  • BMD *improved* with ALN or RIS switch to → denosumab or teriparatide

Sequential PMO Therapy
Switch regimen

**Switch** from risedronate (RIS) to teriparatide

**2 prospective studies:** Assessing treatment after RIS in women with PMO:

- **Duration:** 12 and 24 mos
- **Figures:** % BMD change
  - Lumbar spine – top
  - Total hip – bottom

TPTD, teriparatide. PMO, postmenopausal osteoporosis. BMD, bone mineral density.

Sequential PMO Therapy
Switch regimen

**Switch** from alendronate (ALN) to alternate drug therapy

9 prospective studies: Assessing treatment after ALN in women with PMO

**Duration:** 12, 18, 24 mos

**Figures:** BMD % change from baseline

Add vs switch to TPTD from prior ALN therapy

**Study:** Randomized open label study in women with PMO
ALN therapy (n=102) for at least 18 months prior to teriparatide (TPTD) use (range 3-4 yr use)

**Duration:** 18 mos

**Figures:** L-spine and Total hip BMD % change from baseline

**Outcomes:** With TPTD added to ALN, BCM change less but BMD gain better
Combination Therapy
DATA-Switch Study

Figures: Percent change (%) BMD

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<thead>
<tr>
<th>Years 1-2</th>
<th>Years 3-4</th>
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<tr>
<td>Teriparatide, n=27 ➔ Denosumab</td>
<td>Denosumab, n=27 ➔ Teriparatide</td>
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<tr>
<td>Denosumab, n=27 ➔ Teriparatide</td>
<td>Combination, n=23 ➔ Denosumab</td>
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Conclusions
Effect of teriparatide in orthopedic spine surgery

• After instrumented for lumbar posterolateral fusion
  • Bone fusion rate higher
  • Bone union duration better with longer-duration teriparatide
  • Pedicle screw loosening significantly reduced
  • Mean insertional torque value significantly higher

Limitations – Larger and randomized trials are needed
Conclusions
Effect of teriparatide in treating AFF

- **Bone histomorphometry**
  - Increased bone formation, mineralizing surface, and mineral apposition within 6 months

- **Microarchitecture**
  - Cortical bone mineralization density less (HRpQCT)
  - Bone BCM increased (CTX and P1NP)

- **Fracture healing**
  - Healing of non-union fractures (radiographs / scans), and resolution of pain

**Limitations** – AAF rare, and treatment data is limited
Thank You!
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