Osteoporosis – Sequential Drug Therapy

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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:

- Drug differences in the duration of skeletal antiresorptive effects during a ‘drug holiday’
- Use of antiresorptive and anabolic drugs in sequential or combination therapy for postmenopausal osteoporosis

ASBMR 2015 Task Force Recommendations

Osteoporosis drug holiday

- Postmenopausal women treated with oral (≥5 yrs) or IV (≥3 yrs) bisphosphonates.
- Hip, spine, or multiple other osteoporosis fractures before or during treatment?

- NO – Hip BMD T Score ≤ -2.5 or High Fx risk?
  - NO – Consider a drug holiday*
  - YES – Reassess risks/benefits; consider continuing bisP, or change to alternative therapy*

- YES – Reassess risks/benefits; consider continuing bisP for up to 10 yrs, or change to alternative therapy*

* Reassess every 2 to 3 years.
Objectives

2015 ASBMR Task Force recommendations for an osteoporosis-related ‘drug holiday’

• Drug differences in duration of skeletal antiresorptive effects during a ‘drug holiday’

Bone Remodeling and Bone Turnover Markers (BTMs)

Relationship of BTMs to their origins of bone resorption or bone formation during bone remodeling

Bisphosphonates
Odanacatib
Denosumab
Antiresorptive vs Anabolic Therapy

- The ‘anabolic window’ is the time between onset of bone formation to subsequent onset of bone resorption.

Antiresorptive Therapy and ‘Drug Holidays’
Effect on BMD and BTMs during & after 2-years Rx

<table>
<thead>
<tr>
<th>Bauer DC. JBMR 2011;26(2):239</th>
<th>Alendronate, 5–10 mg/day (b) (n = 437)(^{11})</th>
<th>Risedronate, 5 mg/day (n = 398)(^{14})</th>
<th>Denosumab, 60 mg/6 month (n = 128)(^{15})</th>
<th>Odanacatib, 50 mg/week (n = 20)(^{16})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effects on bone mass</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0- to 24-month change on active treatment</td>
<td>Lumbar spine</td>
<td>6.0%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.0%&lt;sup&gt;*&lt;/sup&gt;</td>
<td>6.5%&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Femoral neck</td>
<td>3.0%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.0%&lt;sup&gt;*&lt;/sup&gt;</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Total hip</td>
<td>2.5%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NA</td>
<td>3.4%&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>12-month change after discontinuation&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Lumbar spine</td>
<td>−1.3%</td>
<td>−0.8%&lt;sup&gt;**&lt;/sup&gt;</td>
<td>−6.5%&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Femoral neck</td>
<td>−0.8%</td>
<td>−1.2%&lt;sup&gt;**&lt;/sup&gt;</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Total hip</td>
<td>−1.3%</td>
<td>NA</td>
<td>−3.5%&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Effects on bone turnover</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0- to 24-month change on active treatment</td>
<td>NTX</td>
<td>−65%&lt;sup&gt;*&lt;/sup&gt;</td>
<td>−53%&lt;sup&gt;*&lt;/sup&gt;</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>sCTX</td>
<td>NA</td>
<td>NA</td>
<td>−65%&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>PINP</td>
<td>NA</td>
<td>NA</td>
<td>−70%&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>12-month change after discontinuation</td>
<td>NTX</td>
<td>23%&lt;sup&gt;**&lt;/sup&gt;</td>
<td>67%&lt;sup&gt;**&lt;/sup&gt;</td>
<td>NA</td>
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<tr>
<td></td>
<td>sCTX</td>
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<td>NA</td>
<td>40%&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>PINP</td>
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<td>NA</td>
<td>40%&lt;sup&gt;d&lt;/sup&gt;</td>
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</tbody>
</table>
Objectives

2015 ASBMR Task Force recommendations for an osteoporosis-related ‘drug holiday’

• Drug differences in duration of skeletal antiresorptive effects during a ‘drug holiday’

• Use of antiresorptive and anabolic drugs in sequential and combination therapy for postmenopausal osteoporosis
  • Switch sequential regimen – to alternate drug
  • Add combination regimen – to present drug
  • Simultaneous combination regimen – at onset

Sequential Antiresorptive – Anabolic Rx:
Switch regimen

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

* Drug switch resulted in significant decline in BTM.

ALN, alendronate. IBN, ibandronate. RIS, risendronate. ZOL, zoledronate. RAL, raloxifene. PMO, postmenopause osteoporosis. P Eiken, Osteoporos Int 05 Oct 2015 [Epub. ahead of print].
Sequential PMO Therapy: Switch regimen

Switch from risedronate (RIS) to teriparatide

Figures: BMD (%) change from baseline

2 prospective studies assessing treatment after RIS in women with postmenopausal OP; 12 and 24 mos. duration

Switch from alendronate (ALN) to alternate drug therapy

9 prospective studies assessing treatment after ALN in women with postmenopausal OP; 12, 18, 24 mos. duration
Combination Antiresorptive – Anabolic Rx
Add Teriparatide (TPTD) regimen

- **Change in BMD**
  - Significant BMD ↑ with TPTD *added to*:
    - Prior estrogen Rx¹
    - Prior alendronate Rx²
    - Prior risedronate Rx³


Combination Antiresorptive – Anabolic Rx
Add Teriparatide to estrogen

- TPTD (25 ug/d, 1-34 hPTH) *added* to estrogen
  - RCT for 3-years, n=17
  - Significant ↑ in BMD and ↓ in vertebral fractures

Combination Antiresorptive – Anabolic Rx
Add Teriparatide to Alendronate (ALN)

- TPDT (20 ug, 1-34 hPTH) added to ALN

<table>
<thead>
<tr>
<th>Treatment</th>
<th>hPTH daily, n=43</th>
<th>hPTH cyclic, n=40</th>
<th>ALN only, n=43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67 ± 7</td>
<td>67 ± 8</td>
<td>71 ± 7</td>
</tr>
<tr>
<td>Years ALN use</td>
<td>2.8</td>
<td>3.5</td>
<td>3.0</td>
</tr>
<tr>
<td>T-score Lsp</td>
<td>-2.9 ± 0.9</td>
<td>-2.8 ± 0.8</td>
<td>-2.9 ± 0.8</td>
</tr>
<tr>
<td>T-score Thip</td>
<td>-2.0 ± 0.9</td>
<td>-2.1 ± 0.7</td>
<td>-1.9 ± 0.8</td>
</tr>
<tr>
<td>Prevalent VFx</td>
<td>51%</td>
<td>45%</td>
<td>49%</td>
</tr>
</tbody>
</table>

Osteoporosis Antiresorptive – Anabolic Rx
Add versus switch to TPTD regimen

- Effect on BTMs
  - BTMs ↑ more with switch to TPTD from prior RAL or ALN therapy
    - vs TPTD add to RAL or ALN

- Effect on BMD
  - BMD ↑ may be greater with TPTD add on regimen,
    - due to a greater ‘anabolic window’ effect?
Add vs switch to TPTD – from prior ALN or RAL

BMD Change
Randomized open label study in PM women with OP
Alendronate - ALN
Raloxifene - RAL
Both ALN and RAL therapy for at least 18 mos prior to TPTD

Switch to TPTD – from prior ALN or RAL

PM, postmenopausal, OP, osteoporosis, AR, antiresorptive. Cosman F, JCEM 2009; 94(10):3772-80

* p<0.05 from baseline. † p<0.05 between Rx’s.

N-propeptide of type-1 collagen
RAL
ALN

Bone specific alkaline phosphatase
RAL
ALN

Lumbar Spine BMD
RAL
ALN

N-telopeptide of collagen
RAL
ALN

Lumbar Spine BMD
RAL: add TPTD
ALN: switch to TPTD

Total Hip BMD
RAL: add TPTD
ALN: switch to TPTD

Lumbar Spine BMD
RAL: add TPTD
ALN: switch to TPTD

Total Hip BMD
RAL: add TPTD
ALN: switch to TPTD
Combination Antiresorptive – Anabolic Rx
Simultaneous onset of TPTD + anti-resorptive Rx

• Studies
  • Teriparatide + raloxifene¹
  • Teriparatide + alendronate²³
  • Teriparatide + zoledronate⁴
  • Teriparatide + denosumab⁵

• Outcomes
  • Primary outcome is change in L-spine BMD
    • No fracture data
    • Studies of short (1-year) duration

Combination Antiresorptive – Anabolic Rx
Simultaneous onset of TPTD + anti-resorptive Rx

• Change in BMD
  • Teriparatide + raloxifene (RAL)¹
    • BMD ↑ greater at Total-hip vs TPTD alone
    * L-spine and femur-neck BMD change ns

Simultaneous onset – teriparatide + raloxifene

**RCT** to compare TPTD+RAL (n=69) vs TPTD alone (n=68)

- **BMD increase** over 6 mos.
  - L-sp ↑ in both groups
  - Hip ↑ only in the TPTD+RAL group
  - **Combined** TPTD+RAL with a greater ↑ at the T-hip than TPTD alone

- **BTM change** over 6 mos.
  - P1NP ↑ similar in both groups
  - CTx ↑ significantly less with TPTD+RAL

Combination Antiresorptive – Anabolic Rx

*Simultaneous onset of TPTD + antiresorptive Rx*

- **Change in BMD**
  - Teriparatide + raloxifene¹
    - BMD ↑ **greater** at Total hip vs TPTD alone
  - Teriparatide + alendronate (ALN)² ³
    - BMD ↑ **variable** vs TPTD alone at the hip
      - TPTD alone with BMD ↓ at cortical bone
      - ALN as 1st line Rx appears to be equal to or better than TPTD alone or TPTD+ALN

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Alendronate + Teriparatide in PM Women
*Simultaneous* onset of TPTD and ALN

238 PM women w/o prior bisphosphonate + low hip or spine BMD

- (T score < -2.5, or T score < -2.0 with another OP risk factor)

Randomly assigned to daily treatment

- rhPTH (1-84) (100 μg; n=119), alendronate (10 mg; n=60), or both (n=59) and followed for 12 months

- Spine and hip BMD assessed by DXA and quantitative CT scan


Femur Bone Structure and Density

USA (Combined NHANES/Lunar) Left Femur: Total (BMD) 0.26 BMD (g/cm²)

Age-Matched T-score

Age (years)

<table>
<thead>
<tr>
<th>Region</th>
<th>BMD (g/cm²)</th>
<th>Young-Adult T-score</th>
<th>Age-Matched T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck Left</td>
<td>0.827</td>
<td>-1.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Total Left</td>
<td>0.840</td>
<td>-1.3</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Combination Antiresorptive – Anabolic Rx

Simultaneous onset of TPTD + antiresorptive Rx

- **Change in BMD**
  - Teriparatide + raloxifene¹
    - BMD ↑ **greater** at Total hip vs TPTD alone
  - Teriparatide + alendronate² ³
    - BMD ↑ **variable** vs TPTD alone at the hip
  - Teriparatide + Zoledronate (ZOL)⁴
    - BMD ↑ **greater** vs TPTD alone
      - Better than TPTD alone at the hip
      - Equal to TPTD alone at the spine
      - Better than ZOL alone at the spine

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Combination Antiresorptive – Anabolic Rx

Simultaneous onset of TPTD and ZOL

Combination Antiresorptive – Anabolic Rx

Simultaneous onset of TPTD + antiresorptive Rx

- Change in BMD
  - Teriparatide + raloxifene¹
    - BMD ↑ greater at Total hip vs TPTD alone
  - Teriparatide + alendronate² ³
    - BMD ↑ variable vs TPTD alone at the hip
  - Teriparatide + Zoledronate⁴
    - BMD ↑ greater vs TPTD alone
  - Teriparatide + Denosumab⁵
    - BMD ↑ best with combination therapy, or TPTD to Dmab; vs Dmab to TPTD switch


Denosumab + Teriparatide in PM Women
The DATA-Switch study

Figures: Change in BTMs
Osteocalcin (bone formation)
C-telopeptide (bone resorption)

<table>
<thead>
<tr>
<th>Years 1-2</th>
<th>Years 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teriparatide, n=27 ➤ Denosumab</td>
<td></td>
</tr>
<tr>
<td>Denosumab, n=27 ➤ Teriparatide</td>
<td></td>
</tr>
<tr>
<td>Combination, n=23 ➤ Denosumab</td>
<td></td>
</tr>
</tbody>
</table>

**Denosumab plus Teriparatide**

**Figures:** BMD change (%)

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**Conclusions**

**Osteoporosis-related ‘drug holiday’**

- Based on FLEX and HORIZON trials
  - *After 3-5 yrs,* management based on Fx risk, to include Fx history and BMD
  - *After 10-yrs,* management in high risk patients as per clinical judgment

- Study limitations
  - Based on ALN and ZOL only
  - Based on VFx reduction
  - In Caucasian women only

ALN, alendronate. ZOL, zoledronic acid. VFx, vertebral fracture.
Conclusions
Sequential/combination therapy

• With prior ALN or RIS antiresorptive (AR) therapy
  • BMD maintained with ALN switch to → RAL, RIS, IBN, or ZOL
  • BMD improved with ALN or RIS switch to → denosumab or teriparatide

• With Teriparatide use
  • Add on to prior AR builds BMD better than switch, especially for short half-life drugs (RAL, Dmab)
  • AR switch to TPTD builds BMD at spine >> hip
  • Combination therapy ensures best overall BMD gain at both spine and hip sites, if drug naïve

Thank You!

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