Duration of Bisphosphonate Rx and Drug Holidays: When, How and If?

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- Consulting or advisory boards:  
  None
- Research agreements:  
  Alexion
Risks and benefits of initiating osteoporosis treatment

**Short-term treatment (3-5 years)**

- Benefits (fracture reductions)
- Risks (ONJ, AFF)
- Benefits vs. risk

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**Summary of Bisphosphonate Fracture Reductions (up to 5 Years)**

<table>
<thead>
<tr>
<th></th>
<th>Alendronate</th>
<th>Risedronate</th>
<th>Ibandronate</th>
<th>Zoledronic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Relative risk reduction, %</td>
<td>Relative risk reduction, %</td>
<td>Relative risk reduction, %</td>
<td>Relative risk reduction, %</td>
</tr>
<tr>
<td>Vertebrae</td>
<td>-80</td>
<td>-60</td>
<td>-40</td>
<td>-20</td>
</tr>
<tr>
<td>Hip</td>
<td>-80</td>
<td>-60</td>
<td>-40</td>
<td>-20</td>
</tr>
</tbody>
</table>

Also reductions ~25% in non-vertebral fractures

Benefits of Therapy: Fractures prevented in 1,000 osteoporotic women treated for 3 years*

<table>
<thead>
<tr>
<th>Fractures prevented</th>
<th>Based on results from large RCTS: FIT, HORIZON, VERT NA, others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine</td>
<td>71</td>
</tr>
<tr>
<td>Non-vertebral</td>
<td>29</td>
</tr>
<tr>
<td>(hip)</td>
<td>(11)</td>
</tr>
<tr>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>

* Like women in FIT, HORIZON trials

Adverse Publicity: Effect on Oral Bisphosphonate Use in USA

Source: IMS Vector One®: National, Years 2002-2012 Data Extracted February 2013

Wysowski DK, Greene P. Bone. 2013;57:423-428
What about Safety?

Impactful recent safety concerns:
- Osteonecrosis of the jaw (ONJ)
- Atypical femur fractures

ONJ and oral Bisphosphonates: Summary from ASBMR report, 2007

- Very rare in osteoporosis patients (1 in 10,000 to 100,000)
  - Higher in oncology use
- Invasive bone procedures (extraction) strongest risk factor. Weaker risk factors include:
  - > age 65, periodontitis, dentures,
- Little evidence that doses used for osteoporosis increase risk of ONJ
  - If so, VERY low risk
- 2012 ADA report (Hellstein et al) has helped to put concerns into perspective
Atypical subtrochanteric fractures: Case Reports and Case Studies

- First identified in case reports and case series (2006-2010)
  - NY and Singapore
- Associated with bisphosphonates?


Morphologic Characteristics of Atypical Femur Fractures from Case Reports

Neviaser et al J. Ortho trauma 2008
ASBMR Task Force on Atypical Femur Fracture (2010/2014*)

• Begun in 2009, first published 2010
• Updated report (2014)
• Careful review of ever-growing literature
• Created a case-definition to standardize reporting and research

*Shane, et. al. JBMR, 2010 & 2013

ASBMR Task Force Case Definition for Atypical Femur Fracture (Update 2014)*

• Major Criteria (must have >4)
  – Location: Below lesser trochanter above distal metaphyseal flare
  – Transverse or short-oblique (from x-ray)
  – Minimal or no trauma
  – Non- or minimally comminuted
  – Localized reaction in lateral cortex

• Minor Criteria (may be present)
  – Increased cortical thickness (generalized)
  – Prodromal symptoms (pain in thigh/groin)
  – Bilateral
  – Delayed healing

*Shane, et. al. JBMR, 2010/2014
What types of Studies Assessing Incidence of AFF and Relationship to BP use?

1) Individual case reports and case series (from 2007)
   • Total > 230 cases published

2) Observational/epidemiologic studies (Canada, Denmark, US, Sweden, other countries)
   • Mostly sets of cases compared to controls
   • A couple of cohort studies

3) A bit of data from RCT’s
   • 2013: meta-analysis of bisphosphonates and atypical fracture (Gedmintas, JBMR, 2013)

2 of the largest epidemiologic studies

1. Swedish study (Schilcher)
2. Kaiser NW, U.S. (Feldstein)

Both:
   - Population based
   - Reviewed individual x-rays from fracture patients

Schilcher et al, NEJM 5/11
Feldstein, JBMR 2012
Swedish study of Bisphosphonates and Atypical Fracture

- All hip/femur fractures in Sweden 2008 (12,777)
- ICD-10 (S722 and S723) in National Register
  - Subtrochanteric or femoral shaft (n=1271)
- 1234 X-rays Retrieved/reviewed for AFF, ASMBR-like criteria
- Link to pharmaceutical register (3 yrs only)

Schilcher et al, NEJM 5/11

Swedish study: How many with AFF?

- 1.5 million Swedish women > age 55
- ~12,777 femur fractures in 2008
- 322 met review criteria for subtrochanteric/FS
  - 59 atypical

59 AFF per 12,700 femur fractures

Schilcher et al, NEJM 5/11
How common are AFF compared to all femur fractures? From Swedish study of Schilcher et al. (NEJM, 2011)

1000 femur fractures

- 110 ICD-coded ST/FS (excl. miscodes, implants)
- 25 true ST/FS
- 5 AFF’s

Number of AFF’s per hip fracture

- Schilcher and Feldstein are only population-based studies with x-ray evaluation
- ASMBR (2010-like) evaluations

<table>
<thead>
<tr>
<th>Study</th>
<th>Hip fractures</th>
<th>AFF fractures*</th>
<th>AFF per 1000 hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schilcher</td>
<td>12,700</td>
<td>59</td>
<td>4.6</td>
</tr>
<tr>
<td>Feldstein</td>
<td>5034</td>
<td>22</td>
<td>4.4</td>
</tr>
</tbody>
</table>

- Use this number to compute risks for BP treatment for 3-5 years
How Strong is relationship of bisphosphonates to AFF fracture risk?

- Wildly varying relative risks for bisphosphonate use

- Schilcher (Swedish) study: Relative risk 33 to > 65 (!)

- Kaiser NW study: Relative risk = 2.1

Feldstein, Black, et al. JBMR 2012: Schilcher NEJM 2011

2013 Meta-analysis of atypical femur fracture studies: 13 case-control and cohort studies*

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-Control</td>
<td></td>
</tr>
<tr>
<td>Feldstein 2012</td>
<td>2.11 (0.99 to 4.49)</td>
</tr>
<tr>
<td>Lenart 2009</td>
<td>15.33 (3.06 to 76.49)</td>
</tr>
<tr>
<td>Meier 2012</td>
<td>65.10 (32.81 to 129.46)</td>
</tr>
<tr>
<td>Park-Wyllie 2011</td>
<td>0.74 (0.23 to 2.01)</td>
</tr>
<tr>
<td>Schilcher 2011</td>
<td>33.30 (14.28 to 77.67)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>11.12 (2.68 to 46.18)</td>
</tr>
<tr>
<td>Cohort</td>
<td></td>
</tr>
<tr>
<td>Ahlbomsson 2009</td>
<td>1.46 (0.91 to 2.35)</td>
</tr>
<tr>
<td>Ahlbomsson 2010</td>
<td>2.18 (1.78 to 2.66)</td>
</tr>
<tr>
<td>Black (FIT) 2010</td>
<td>1.63 (0.96 to 2.68)</td>
</tr>
<tr>
<td>Black (FLEX) 2010</td>
<td>1.33 (0.12 to 14.71)</td>
</tr>
<tr>
<td>Black (HORIZON-PFT) 2010</td>
<td>1.29 (0.25 to 9.00)</td>
</tr>
<tr>
<td>Vestergaard 2011</td>
<td>1.63 (0.70 to 1.52)</td>
</tr>
<tr>
<td>Kim 2011</td>
<td>2.41 (1.78 to 3.27)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>1.52 (1.28 to 2.15)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.70 (1.22 to 2.37)</td>
</tr>
</tbody>
</table>

Compute Risks for AFF: Assumptions

• Incidence of AFF: 5 AFF per 1000 femur fractures

• Vary assumptions for relative risk of BP use and AFF.
  
  – Meta analysis: 1.7 (1.2, 2.4)*
  
  – Other sources: 11.8

Gedmintas, JBMR 2013
Black, Rosen. NEJM. Osteoporosis Review, 1/2016

Scenario:
Treat 1,000 osteoporotic women for 3 years
## Benefits vs. Risks of BP Treatment

**Table 3. Number of Patients Who Would Need to Be Treated for 3 Years with Bisphosphonates to Prevent One Fracture versus the Hypothetical Number Associated with an Increase of One Atypical Femur Fracture.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. Needed to Treat (3 yr)</th>
<th>No. of Events Prevented per 1000 Patients Treated (3 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any nonvertebral, including hip</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>Hip</td>
<td>90</td>
<td>11</td>
</tr>
<tr>
<td>Vertebral fracture (morphometric)</td>
<td>14</td>
<td>71</td>
</tr>
<tr>
<td>Any fracture</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Hypothetical relative risk of atypical femur fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2</td>
<td>43,300</td>
<td>0.02</td>
</tr>
<tr>
<td>1.7</td>
<td>12,400</td>
<td>0.08</td>
</tr>
<tr>
<td>2.4</td>
<td>6,200</td>
<td>0.16</td>
</tr>
<tr>
<td>11.8</td>
<td>800</td>
<td>1.25</td>
</tr>
</tbody>
</table>

*Black, Rosen. NEJM 1/16*

## Treat 1000 osteoporotic women for 3 years:

- Prevent: 100 fractures including 11 hip fracture
- Cause: .02 to 1.2 AFF

*Black, Rosen. NEJM 1/16*
Benefits for BP (and other osteoporosis treatment) (for 3-5 years) far outweigh any risks, even allowing for some risk of AFF.

What about treatment beyond 5 years?.... Stay tuned.

Randomized Extension Studies for Alendronate and ZOL

- **HORIZON-PFT**
  - ZOL (n = 3889)
  - PBO (n = 3876)

- **RCT – EXT1**
  - ALN (n = 616)
  - Z3P3 (n = 617)

- **RCT – EXT2**
  - Z9 (n = 95)
  - Z6P3 (n = 95)

**Alendronate**

- **FIT4**
  - ALN (n = 3236)
  - PBO (n = 3223)

- **RCT – FLEX**
  - ALN 5 mg (n = 332) or 10 mg (n = 333)
  - PBO (n = 437)

**Zoledronic acid**

- **HORIZON-PFT1**
  - ZOL (n = 3889)
  - PBO (n = 3876)

- **RCT – EXT12**
  - ALN 5 mg (n = 330) or 10 mg (n = 333)
  - PBO (n = 437)

- **RCT – EXT8**
  - RIS (n = 135)
  - PBO (n = 130)

- **OL-EXT9**
  - RIS 7 yrs (n = 83)
  - PBO 5 yrs/RIS 2yrs (n = 81)
Design of the FIT Long-Term Extension (to 10 years) of Alendronate (FLEX)*

**FIT**  N = 6,459

- **Placebo**  N = 3,223
- **Alendronate**  N = 3,236

**Mean ALN use:**
- 5 years

**Randomized in FLEX**  N = 1,099

- **Placebo**  N = 437
- **Alendronate, 5 or 10 mg**  N = 662

**BMD: Primary endpoint**

**Fractures: Exploratory endpoint**


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**FLEX: Alendronate**

*Randomized, Double-blind Treatment*

*5 years of ALN followed by 5 more years or PBO*

**FLEX: Incidence of Fracture by Treatment Group**

<table>
<thead>
<tr>
<th>Fractures</th>
<th>Placebo, No. (%) (n=437)</th>
<th>Pooled Alendronate, No. (%) (n=662)</th>
<th>Relative Risk (95% Confidence Interval) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Morphometric</td>
<td>23 (5.3)</td>
<td>46 (11.3)</td>
<td>0.45 (0.24–0.85)</td>
</tr>
<tr>
<td>Clinical Hip</td>
<td>46 (11.3)</td>
<td>60 (9.8)</td>
<td>0.86 (0.60–1.22)</td>
</tr>
<tr>
<td>Nonspine Hip</td>
<td>83 (19.0)</td>
<td>125 (18.9)</td>
<td>1.00 (0.76–1.32)</td>
</tr>
<tr>
<td>Clinical Nonspine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonspine Morphometric</td>
<td>12 (2.8)</td>
<td>20 (3.0)</td>
<td>1.02 (0.51–2.10)</td>
</tr>
</tbody>
</table>

Fracture reductions with long-term continuation of bisphosphonates (2 RCTs)

- Fracture results for Alendronate and Zol
  - Continuing lowers vertebral fractures risk vs discontinuing
  - Continuing vs. discontinuing → no effect on non-vertebral
    * Confidence intervals are wide and allow for possible benefit

- What about long term safety? Does AFF risk increase with longer duration of treatment?
What about long term safety? Does AFF risk increase with longer duration of treatment?

- Very controversial question

- 2012 Kaiser SC case series of AFF
  - Influential but methodologic flaws

- 2016 Danish cohort study
  - Used subtrochanteric/femoral shaft fractures (not adjudicated AFF)
  - Suggests benefits vs. risks strongly favorable for long term treatment

Do Atypical Femur Fractures Increase with Duration of Treatment? AFF cases from Kaiser S. Calif*

![Graph showing incidence of AFF vs. years of use of bisphosphonates](Dell et. al. JBMR 12/12)
Do Atypical Femur Fractures Increase with Duration of ALN Treatment? Recent Danish Cohort (81,000 users)*

ST/FS: Subtrochanteric/Femoral Shaft fracture

Is AFF incidence increased with longer duration of use?

- Results are mixed, not certain
- Most prudent belief: AFF risk increases with treatment duration
- Therefore, best to minimize length of treatment
  And continue to treat only those who will most benefit from longer term treatment

Abrahamsen, et al BMJ 6-16
Which patients benefit most from continuation of ALN (or ZOL) and should therefore be continued?

- Primary benefit is in reduction of vertebral fractures
- Therefore, logical to continue those at highest risk of vertebral fractures
  - NEJM; 5/2012
    * Perspective from FDA together with an analysis from FLEX
  - Consider femoral neck BMD and vertebral fracture status at the end of the initial treatment period

Black, et al. NEJM 2012 May 31;366(22):2051-3

FLEX vertebral fracture benefit:

Who to continue?

<table>
<thead>
<tr>
<th>Femoral Neck BMD T-Score (start FLEX)</th>
<th>Yr risk (%) Clinical Vert Fract In PBO</th>
<th>Number Needed to Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women in study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All BMD values</td>
<td>5.5</td>
<td>34</td>
</tr>
<tr>
<td>≤ -2.5</td>
<td>9.3</td>
<td>21</td>
</tr>
<tr>
<td>-2.5 to -2</td>
<td>5.8</td>
<td>33</td>
</tr>
<tr>
<td>≥ -2</td>
<td>2.3</td>
<td>81</td>
</tr>
<tr>
<td>No prevalent vert. fracture (start of FLEX)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ -2.5</td>
<td>8.0</td>
<td>24</td>
</tr>
<tr>
<td>-2.5 to -2</td>
<td>3.0</td>
<td>63</td>
</tr>
<tr>
<td>≥ -2</td>
<td>1.8</td>
<td>102</td>
</tr>
<tr>
<td>Prevalent vertebral fracture (start of FLEX)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ -2.5</td>
<td>11.1</td>
<td>17</td>
</tr>
<tr>
<td>-2.5 to -2</td>
<td>11.1</td>
<td>17</td>
</tr>
<tr>
<td>≥ -2</td>
<td>3.7</td>
<td>51</td>
</tr>
</tbody>
</table>

Black, et al. NEJM. 2012 May 31;366(22):2051-3
Which patients benefit most from long term ALN (up to 10 years) and should therefore be continued?

- Our recommendations from FLEX* (5 years previous ALN). Continue alendronate in:
  - Women with femoral neck BMD T-score <-2.5
  - In women with existing vertebral fractures, continue treatment in those with fn BMD T-score <-2.0
  - Others can discontinue with retention of some benefits for up to 5 years

*Black, et al. NEJM 5/12

Other clinical factors to assess to decide on discontinuation?

Age (RR=1.5 per 6 years in FLEX)
Fracture on initial phase of treatment (some support)*

Who to continue: Older patients with low hip BMD, and/or vertebral fractures and/or those who fracture during initial treatment

ASBMR committee Fall 2014: Likely to recommend to continue those with hip BMD < -2.5 or "high risk of fracture"

* Cosman et al. ASBMR 2012.
What to do after the ‘holiday’

Or Re-entry Dilemma!!

When to restart?

- Discontinue for no more than 5 years
- *Perhaps* BMD change after 3 to 5 year holiday (not 1 or 2 years)
- No evidence to support bone marker assessment or change in bone marker
Does Osteoporosis Therapy Invalidate FRAX for Fracture Prediction?

William D Leslie, Lisa M Lix, Helena Johansson, Anders Oden, Eugene McCloskey, and John A Kanis for the Manitoba Bone Density Program

WOMEN AGED 20 YEARS WITH BASELINE BMD (n = 38,995)

EXCLUDED (Total = 7,093)
- BMD DONE BEFORE 1990, n = 1,413
- LESS THAN ONE YEAR OBSERVATION, n = 409
- MISSING FEMORAL NECK BMD, n = 2,468
- MISQUALIFIED MASS INDEX, n = 9

POPULATION AVAILABLE FOR ANALYSIS (n = 31,804)

LOST TO FOLLOW UP (Total = 3,299)
- DEATH, n = 2,442
- MIGRATION OUT OF PROVINCE, n = 955

DATA AVAILABLE FOR ANALYSIS
- DEMOGRAPHICS, n = 31,764
- FRACURE OUTCOMES, n = 31,764
- OSTEOPOROSIS MEDICATION USE, n = 31,764
- FRAX PROBABILITY, n = 31,764

ROC Curves For Fracture

Table 2. Area Under the Receiver Operating Characteristic Curve for Fracture Prediction

<table>
<thead>
<tr>
<th></th>
<th>High adherence</th>
<th>Low adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>current treatment</td>
<td>current treatment</td>
</tr>
<tr>
<td>Untreated</td>
<td>(MPR ≥ 0.8)</td>
<td>(MPR &lt; 0.8)</td>
</tr>
<tr>
<td>Prediction of major osteoporotic fractures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major fracture probability without BMD</td>
<td>0.63 (0.61-0.65)</td>
<td>0.67 (0.65-0.69)</td>
</tr>
<tr>
<td>Major fracture probability with BMD</td>
<td>0.66 (0.64-0.68)</td>
<td>0.64 (0.62-0.66)</td>
</tr>
<tr>
<td>Femoral neck BMD</td>
<td>0.65 (0.62-0.67)</td>
<td>0.65 (0.63-0.67)</td>
</tr>
<tr>
<td>Prediction of hip fractures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip fracture probability without BMD</td>
<td>0.78 (0.74-0.82)</td>
<td>0.76 (0.72-0.79)</td>
</tr>
<tr>
<td>Hip fracture probability with BMD</td>
<td>0.82 (0.79-0.85)</td>
<td>0.80 (0.77-0.83)</td>
</tr>
<tr>
<td>Femoral neck BMD</td>
<td>0.78 (0.74-0.83)</td>
<td>0.77 (0.73-0.8)</td>
</tr>
</tbody>
</table>

Data are AUROC (95% CI). MPR = medication possession ratio; BMD = bone mineral density.
BMD One year after Discontinuation of BP

BTMs one year after stopping Aln
Summary of Change in BMD and Risk of Fracture

Long-term treatment: Controversies and unresolved questions..

- Does longer term treatment ...
  - Increase risks?
  - Decrease Benefits?

- Value of drug holidays to reduce risks

- Can we identify those at higher risks? If yes, then use shorter term therapy
  - Promising leads..
    - Asians (RR=5-10)
    - Femoral geometry (more bowed femurs)
Take Home Message

• Drug holidays are a reality even though efficacy not clear
• Should be considered in long term bisphosphonate users
• Assess after the end of the holiday-
  – BMD, bone turnover markers, others
• Restart Rx or add new drug still conjecture

On Shaky Ground?

Very Little Evidence

“First do no harm”