Update in Therapy: Bisphosphonate Holidays

Steven Ing, MD, MSCE

Metabolic Bone Update

11/18/2011
“Be sure to take this drug exactly as directed:
tilt your head to the right at a 37 degree angle, extend
your tongue precisely 4.93182 inches past the furthest
point of the upper lip, place the pill directly between the
48th and 49th taste bud on the left side of the tongue...”

www.DoctorFunnyBone.com
Outline

- Review data on effect of withdrawing anti-osteoporotic agents
- Candidates for a drug holiday
- Duration of drug holiday
Clinical Case

- 60 year old woman with osteopenia, referred for worsening BMD
  - Postmenopausal age 54
  - No prior fractures, no other fracture risks
  - Alendronate started ~2001, stopped 8/2011

<table>
<thead>
<tr>
<th>Date</th>
<th>Lumbar Spine</th>
<th>Total Hip</th>
<th>Femoral Neck</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/1/2000</td>
<td>-0.2</td>
<td>-2.0</td>
<td>-2.1</td>
</tr>
<tr>
<td>5/6/2003</td>
<td>-0.2 (+0.3%)</td>
<td>-1.8 (+3.6%)</td>
<td>-2.1</td>
</tr>
<tr>
<td>2/11/2008</td>
<td>-0.4 (+0.8%)</td>
<td>-1.7 (+0.1%)</td>
<td>-2.0</td>
</tr>
<tr>
<td>7/28/2011</td>
<td>-0.7 (-4.6%)</td>
<td>-1.8 (-2.6%)</td>
<td>-2.2</td>
</tr>
</tbody>
</table>
Definition: Drug Holiday

- Interval of time when a chronically medicated patient temporarily stops taking the medication
  - to allow some recuperation of normal function
  - to maintain sensitivity to the drug
  - to rescue the likelihood of side-effects

WEB MD Medical Dictionary
Loss in BMD after Withdrawal

Estrogen

PTH

Black NEJM 2005;353:555-565
Bisphosphonates and Drug Holiday

- Avid binding to bone tissue
- Long residual tissue residence
- Slow offset of treatment effect

NEJM 2004;350(12):1172-1174
Motivation for Drug Holiday

Possible side effects of long-term treatment
- Atypical femur fracture (later session)
- Osteonecrosis of the jaw
- Esophageal Cancer
ONJ

- **Definition**
  - Current or previous bisphosphonate therapy
  - Exposed bone in the maxillofacial region persisting >8 weeks
  - No history of radiation therapy to the jaw

- **Risk Factors**
  - Usually at site of prior invasive dental surgery
  - IV BP therapy in cancer patient (1-5%)
  - Longer duration of BIS treatment
  - Steroids

- **Symptoms**
  - Pain, swelling, ulceration
  - Paresthesia
  - Suppuration
  - Sinus tracks
  - Loosening of Teeth


ASBMR Task Force, JBMR 2007
ONJ in Osteoporosis

- ZOL: 1 case in active, 1 case in placebo
- No cases identified in other RCTs (60,000 per-yrs)
- ~190 million Rx for ALE, RIS, IBN in US,
  6 million Rx for IV BP for cancer worldwide
- 1:10,000 (Australia)
- 1:250,000 (Germany)
- 1:10,000 - 1:100,000 pt-yrs for oral BP

Felsonberg, Deutsches Arzteblatt 2006;103(46):A3078-3080
Khosla JBMR 2007;22(10):1479-1491
Cross-sectional survey at KPNC

- 8572 patients responded (62%)
- Dental symptoms:
  - periodontal disease, gingival/palatal sores, exposed bone, complications after invasive dental procedures, persistent sx of gums, teeth or jaw
- 2159 patients reported symptoms
  - offered dental exam, records review
- Highly suspicious cases examined and adjudicated by oral surgeon
- Prevalence: 0.1% (0.05-0.2%)
- Frequency: 28 per 100,000 per-yrs

BP and Esophageal Cancer

- **Retrospective Cohort Study (GPRD)**
  - 1995-2005
  - HR 1.07 (0.77-1.49) adjusted for BMI, EtOH, smoking, HRT, NSAID, Barrett’s, GERD, H2B
  - Duration of BP did not change risk of cancer

- **Case-Control (GPRD)**
  - 1996-2006
  - RR 1.30 (1.02-1.66)
  - ≥10 Rx: RR 1.93 (1.37-2.70)
  - 1-9 Rx: RR 0.93 (0.66-1.31)
  - >3 years: RR 2.24 (1.47-3.43)

- **Evidence is inconclusive**

Cardwell JAMA 2010;304(6):657-63
Green BMJ 2010;341:4444
## Bisphosphonate RCTs & Fracture Efficacy

<table>
<thead>
<tr>
<th>Agent</th>
<th>Vertebral Fracture</th>
<th>Hip Fracture</th>
<th>Nonvertebral Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>Yes&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;3,4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Yes&lt;sup&gt;5,6&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;5,7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Yes&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Not shown</td>
<td>Not shown</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>Yes&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

1. Black, Lancet 348:1535-1541
2. Cummings, JAMA 280:2077-2082
3. Black, JCEM 85:4118-4124
4. Pols, Osteoporos Int 9:431-468
5. Harris, JAMA 282:1344-1352
6. Reginster, Osteoporos Int 11:83-91
8. Chestnut, JBMR 19:1241-1249
Extrapolation to the US female population, bisphosphonate tx with adherence ≥50% prevented 144,670 fractures

Siris, JBMR 2011;26(1):3-11
## Bisphosphonates May Decrease Mortality

<table>
<thead>
<tr>
<th></th>
<th>Mortality Rate per 100 per-yrs</th>
<th></th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bisphosphonate</td>
<td>No Treatment</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>0.8 (0.4-1.4)</td>
<td>3.5 (3.1-3.8)</td>
<td>0.27 (0.15-0.50)</td>
</tr>
<tr>
<td>Men</td>
<td>1.0 (0.3-3.9)</td>
<td>4.30 (3.9-4.8)</td>
<td>0.27 (0.07-1.00)</td>
</tr>
</tbody>
</table>

Center, JCEM 2011;96(4):1006-1014
Bisphosphonate Withdrawal
### Alendronate Withdrawal

**FLEX: 5 year extension of FIT**

<table>
<thead>
<tr>
<th>FIT I</th>
<th>FIT 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Yr</td>
<td>4 Yr</td>
</tr>
<tr>
<td>+ Vert Fx</td>
<td>- Vert Fx</td>
</tr>
<tr>
<td>N=2027</td>
<td>N=4432</td>
</tr>
</tbody>
</table>

**Re-randomization**

<table>
<thead>
<tr>
<th>FIT (years 0 to 4)</th>
<th>Post FIT Interval Period</th>
<th>FLEX (years 0 to 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Duration of therapy prior to FLEX (3-6 yrs)</td>
<td>n=1099</td>
<td></td>
</tr>
<tr>
<td>Alendronate (ALN) 5 mg → 10 mg</td>
<td>Drug at no charge or guided by HCP</td>
<td>ALN 5 mg (n=329)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ALN 10 mg (n=333)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PBO (n=437)</td>
</tr>
<tr>
<td>Placebo (PBO)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Black JAMA 2006;296:2927-38
Schwartz AV JBMR 2010;25(5):976-982
## FLEX: Fracture Results

<table>
<thead>
<tr>
<th>Fracture Site</th>
<th>Placebo %</th>
<th>Alendronate %</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphometric Spine</td>
<td>11.3</td>
<td>9.8</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.60-1.22)</td>
</tr>
<tr>
<td>Clinical Spine</td>
<td>5.3</td>
<td>2.4</td>
<td><strong>0.45</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.24-0.85)</td>
</tr>
<tr>
<td>Hip</td>
<td>3.0</td>
<td>3.0</td>
<td>1.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.51-2.10)</td>
</tr>
<tr>
<td>Forearm</td>
<td>4.3</td>
<td>4.7</td>
<td>1.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.62-1.96)</td>
</tr>
<tr>
<td>Nonspine</td>
<td>19.0</td>
<td>18.9</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.76-1.32)</td>
</tr>
<tr>
<td>Any</td>
<td>21.3</td>
<td>19.9</td>
<td><strong>0.93</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.71-1.21)</td>
</tr>
</tbody>
</table>

Black DM et. al., JAMA 2006;296:2927-2938
Nonspine Fracture Risk: Interaction with BMD

p-value for interaction 0.019

Schwartz AV JBMR 2010;25(5):976-982
Fractures after Risedronate withdrawal

Watts NB Osteopor Int 2008;19:365-372
# Fractures after Zoledronic Acid Withdrawal

## Treatment, CORE Years 0-3, EXTENSION Years 4-6

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CORE</th>
<th>EXTENSION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Years 0-3</td>
<td>Years 4-6</td>
</tr>
<tr>
<td>ZA/ZA (Z6)</td>
<td>10.1% (62/616)</td>
<td>8.6% (53/616)</td>
</tr>
<tr>
<td>ZA/Placebo (Z3P3)</td>
<td>9.6% (59/617)</td>
<td>12.0% (74/617)</td>
</tr>
<tr>
<td>Background Placebo</td>
<td>20%</td>
<td>Difference 3.4% (p=0.05)</td>
</tr>
</tbody>
</table>

- **Morphometric spinal fxr:**
  - Z6 vs. Z3P3: RR=0.48, p=0.04
- **Clinical spine, hip, non-vertebral fxr:** NS

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FDA Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee
9/9/2011 Meeting
### Summary of Fracture Data

<table>
<thead>
<tr>
<th>Fracture</th>
<th>Alendronate</th>
<th>Risedronate</th>
<th>Zoledronic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphometric Spine</strong></td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td><strong>Clinical Spine</strong></td>
<td>Reduced</td>
<td>Not reported</td>
<td>---</td>
</tr>
<tr>
<td><strong>Non-Spine</strong></td>
<td>Reduced in T≤2.5 (w/o vertebral fxr)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
## FDA Pooled Fracture Data

<table>
<thead>
<tr>
<th></th>
<th>Year 0-3</th>
<th>Year 4-5</th>
<th>Year 6-9</th>
<th>Year &gt;9</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 Fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous Active Tx</td>
<td>9.7% (117/1200)</td>
<td>6.0% (72/1200)</td>
<td>10.6% (62/585)</td>
<td>9.3% (48/517)</td>
</tr>
<tr>
<td>(ALN+ZOL+RIS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 Fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Yr Active Tx then</td>
<td>8.2% (79/968)</td>
<td>8.6% (83/968)</td>
<td>8.8% (31/351)</td>
<td>8.0% (28/351)</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active Tx</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Background Placebo</td>
<td>20.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FDA Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee 9/9/2011 Meeting
“In light of all the risk-benefit challenges with the bisphosphonate class, these data suggest that bisphosphonate therapy could be safely discontinued from an efficacy standpoint. However, additional long-term data would be needed to further define an appropriate duration of drug cessation and to determine if interim monitoring is appropriate on an individual basis.”

“There are no substantial data available to inform decision regarding the initiation or duration of a drug holiday.”
Low Fracture Risk

- 53 year old woman
- Menopause age 50
- T-score -1.6
- No other fracture risk factors
- Bisphosphonate x 2 years

- Tx not indicated initially
- Stop tx
Mild Fracture Risk

- 65 year old woman
- Menopause age 52
- T-score -2.6
- No other fracture risk factors
- Bisphosphonate x 5 years
- T-score now -2.3

- Tx indicated initially
- Consider drug holiday
Moderate Fracture Risk

- 70 year old woman
- Menopause age 49
- T-score -2.7
- No other fracture risks
- Bisphosphonate x 8 years
- T-score now -2.3

- Tx indicated initially
- Consider drug holiday
High fracture risk

- 72 year old woman
- Menopause age 43
- T-score -3.8
- Rheumatoid arthritis on steroid therapy x 12 years
- 2 vertebral fractures
- Bisphosphonate x 10 years

- Tx indicated initially
- Continued high fracture risk
- ? Switch to teriparatide or raloxifene
Clinical Case (cont’d)

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: US (Caucasian)

1. Age (between 40-90 years) or Date of birth
   Age: [ ]
   Date of birth: [ ]

2. Sex
   [ ] Male
   [ ] Female

3. Weight (kg)
   [ ]

4. Height (cm)
   [ ]

5. Previous fracture
   [ ] No
   [ ] Yes

6. Parent fractured hip
   [ ] No
   [ ] Yes

7. Current smoking
   [ ] No
   [ ] Yes

8. Glucocorticoids
   [ ] No
   [ ] Yes

9. Rheumatoid arthritis
   [ ] No
   [ ] Yes

10. Secondary osteoporosis
    [ ] No
    [ ] Yes

11. Alcohol 3 or more units per day
    [ ] No
    [ ] Yes

12. Femoral neck BMD (g/cm²)

   T-Score: -2.2

   [ ] Clear
   [ ] Calculate

BMI 26.6
The ten year probability of fracture (%)

with BMD
- Major osteoporotic: 10
- Hip fracture: 1.6

Weight Conversion

Pounds  [ ] kg

150 [ ] Convert

Height Conversion

Inches  [ ] cm

63 [ ] Convert

00449443
Individuals with fracture risk assessed since 1st June 2011
Monitoring on Drug Holiday

- Bone Mineral Density?
- Bone Turnover Markers?
BMD after Stopping Alendronate

FOSAMAX: FIT/FLEX Studies – All FLEX Patients

FEMORAL NECK

LUMBAR SPINE

Black DM et. al., JAMA 2006;296:2927-2938
BMD after stopping Zoledronic Acid

ASBMR 2010 #1070 Black et al.
BTM after stopping Alendronate

Black DM et. al., JAMA 2006;296:2927-2938
BTM after RIS withdrawal

Watts NB Osteopor Int 2008;19:365-372
Strategy #1: Fixed Interval

- Because important fractures appear to increase within 1-5 years of stopping therapy
  - Limit alendronate holiday to 2 years
  - Limit risedronate holiday to 1 year
- At those time points, reevaluate the question of whether the patient is a candidate for therapy
  - NO: reevaluate later
  - YES: consider retreatment, but not necessarily BIS

McClung, 2011 ASMBR
Strategy #2: Monitoring

- Some individuals show rapid decreases in BMD after stopping bisphosphonate therapy
  - in FLEX, thresholds were >8% in 1 year, >10% in 2 years, or >5% from baseline
  - those rapidly losing BMD will likely require resumption of bisphosphonate therapy or starting to alternative agent

- Following BTMs is more appealing, but we do not know how to do this based on current data
  - In RIS study, fracture reduction persists despite rise in BTMs
Drug Holiday: FDA

“additional data are needed to further define an appropriate duration of drug holiday and to determine whether interim monitoring could be informative.”
What Data Do We Need?

- Clinical trial of fracture risk in pt tx 3-5 years and randomize vs. stop tx
  - Many pts and very expensive
- Analyze individual responses in existing clinical trial cohorts to assess the distribution of responses to stopping therapy
“The Lord will guide you continually, and satisfy your needs in parched places, and make your bones strong; and you shall be like a watered garden, like a spring of water, whose waters never fail.”

Isaiah 58:11