What to Do after Drug Holidays

Clifford Rosen MD
rosenc@mmc.org

No Conflicts of Interest

What To Do After Drug Holidays

- Overview of Drug Holidays
  - Who to stop, who to continue, who to send on vacation
- How to Assess Risk after a ‘Holiday’
  - Gestalt
  - DXA
  - Bone Markers
  - What the patient wants
- What to do about treatment?
  - Anti-resorptive
  - Anabolic

Bisphosphonate Scripts in the US
Over the last 2 decades
A drug holiday (sometimes also called a drug vacation, medication vacation, structured treatment interruption or strategic treatment interruption) is when a patient stops taking a medication(s) for a period of time; anywhere from a few days to many months or even years if they feel it is in their best interests.

How Do Bisphosphonates Work?

Bisphosphonates may modulate signaling from osteoclasts to osteoblasts
- Increased OPG production
- Decreased RANKL expression
- New bone
- Bone

Bisphosphonates are concentrated under osteoclasts

Bisphosphonates inhibit osteoclast activity, and promote osteoclast apoptosis

Studies of Long Term Bisphosphonate Use (BMD primary endpoint)

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug Design</th>
<th>N</th>
<th>Follow-up years</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIT Long-Term Extension (FLEX)</td>
<td>Alendronate (5 &amp; 10 mg/day) Randomized blinded trial</td>
<td>1099</td>
<td>5+5=10</td>
<td></td>
</tr>
<tr>
<td>HORIZON-PFT Ext.</td>
<td>Zoledronic acid (5 mg/year) Randomized blinded trial</td>
<td>1233</td>
<td>3+3=6</td>
<td></td>
</tr>
<tr>
<td>Risedronate weekly</td>
<td>Observation study</td>
<td>164</td>
<td>3+3+3=9</td>
<td>Small, non-randomized, adherent only</td>
</tr>
</tbody>
</table>

Efficacy of Bisphosphonates for Reducing Clinical Fracture

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial</th>
<th>Active</th>
<th>Placebo</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALN*</td>
<td>FIT II(T&lt;2.5)</td>
<td>15.3%</td>
<td>9.9%</td>
<td>18</td>
</tr>
<tr>
<td>ZOL**</td>
<td>HOR PFT</td>
<td>13.3%</td>
<td>8.3%</td>
<td>20</td>
</tr>
</tbody>
</table>

* Black et al JCEM 2000  **Black et al NEJM 2007
Design of the FIT Long-Term Extension of Alendronate (FLEX)*

Primary endpoint: Change in hip BMD

FIT (3 to 4.5 yrs)

Post-FIT (1-2 yrs)

FLEX (5 yrs)

Randomized in FLEX
N = 1,099

Placebo  N = 437

Alendronate, 5 mg  N = 329

Alendronate, 10 mg  N = 333

Placebo   N = 3,223

Alendronate N = 3,236

FLEX (5 yrs)

Placebo  N = 437

Alendronate, 5 mg  N = 329

Alendronate, 10 mg  N = 333


Total Hip BMD: Mean % Change from FIT Baseline

Fracture Incidence (Exploratory Endpoint) In FLEX

Vertebral

Clinical

Morphometric

Clinical

Any

Non-vertebral

Hip

PBO  (N = 437)

ALN  (N = 662)

RR (95% CI)

5%

2%

0.45 (0.2, 0.8)

11.3%

9.8%

0.86 (0.6, 1.2)

22%

21%

0.93 (0.7, 1.2)

20%

19%

1.00 (0.8, 1.4)

3%

3%

1.02 (0.5, 2.3)

Survival Curve for Time to First Nonvertebral Fracture in FLEX

HORIZON Extension Study Design

- Similar to FLEX extension
- 3 years of annual ZOL, then randomized to either:
  - 3 more years of ZOL (6 years, Z6)
  - 3 years of PBO (Z3P3)

Fracture Results in HORIZON PFT Extension: 3 more years of ZOL

<table>
<thead>
<tr>
<th></th>
<th>Z3P3 (N = 616)</th>
<th>Z6 (N = 617)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>0.7%</td>
<td>1.2%</td>
<td>1.8 (0.5, 6.2)</td>
</tr>
<tr>
<td>Morphometric</td>
<td>6%</td>
<td>3%</td>
<td>0.48 (0.3, 0.9)</td>
</tr>
<tr>
<td>Non-vertebral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-vertebral</td>
<td>7.6%</td>
<td>8.2%</td>
<td>0.99 (0.7, 1.5)</td>
</tr>
<tr>
<td>Hip</td>
<td>1.4%</td>
<td>1.3%</td>
<td>0.90 (0.3, 2.5)</td>
</tr>
</tbody>
</table>

* Black, et al, JBMR 2012

Summary of Vertebral Fracture Reductions for FLEX and HORIZON

Efficacy from the 2 long-term randomized extension studies

- Fracture results for both drugs
  - Continuing lowers vertebral fractures risk vs discontinuing
  - Continuing vs. discontinuing ➔ no effect on non-vertebral
    • Confidence intervals are wide and allow for possible benefit

- BMD results for both drugs (ALN and ZOL):
  - Continuing long term ➔ retains BMD gains
  - Discontinuing ➔ BMD loses are modest

- What about long term safety? Does AFF risk increase with longer duration of treatment?
**FLEX vertebral fracture benefit:**

**Who to continue?**

<table>
<thead>
<tr>
<th>All women in study</th>
<th>Femoral Neck BMD T-score (start FLEX)</th>
<th>5 Yr risk (%) Clinical Vert. Fr. in PBO</th>
<th>Number Needed to Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All BMD values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ -2.5</td>
<td>9.3</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>2.5 to -2</td>
<td>5.8</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>&gt; -2</td>
<td>2.3</td>
<td>81</td>
<td></td>
</tr>
</tbody>
</table>

No prevalent vert. fracture (start of FLEX)

| ≤ -2.5             | 8.0                                  | 24                                     |                        |
| 2.5 to -2          | 3.0                                  | 62                                     |                        |
| > -2                | 1.8                                  | 102                                    |                        |

Prevalent vertebral fracture (start of FLEX)

| ≤ -2.5             | 11.1                                 | 17                                     |                        |
| 2.5 to -2          | 15.1                                 | 17                                     |                        |
| > -2                | 57.7                                 | 51                                     |                        |

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

---

Which patients benefit most from long term 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

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
One year after Discontinuation of BP

Summary of Change in BMD

Table 4. Change in Bone Mineral Density (BMD) or Bone Turnover Markers (BTMs) and Subsequent Age-Adjusted Risk of Clinical Fracture After Discontinuation of Alendronate Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>1-Year Change</th>
<th>2-Year Change</th>
<th>3-Year Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral neck</td>
<td>0.36 (0.61-1.56)</td>
<td>1.54 (0.93-2.44)</td>
<td>1.32 (0.77-2.28)</td>
</tr>
<tr>
<td>Total hip</td>
<td>1.07 (0.98-1.16)</td>
<td>1.56 (0.97-2.52)</td>
<td>1.68 (0.98-2.86)</td>
</tr>
<tr>
<td>Spine</td>
<td>NA</td>
<td>NA</td>
<td>1.11 (0.61-1.97)</td>
</tr>
<tr>
<td>10th percentile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral neck</td>
<td>1.12 (0.70-1.60)</td>
<td>1.45 (0.80-2.53)</td>
<td>1.39 (0.83-2.26)</td>
</tr>
<tr>
<td>Total hip</td>
<td>1.26 (0.83-1.93)</td>
<td>1.68 (1.05-2.72)</td>
<td>1.63 (0.95-2.37)</td>
</tr>
<tr>
<td>Spine</td>
<td>NA</td>
<td>NA</td>
<td>0.77 (0.35-1.64)</td>
</tr>
</tbody>
</table>

BTMs one year after stopping Aln

What To Re-Start or Maintain?

How About Calcium and Vitamin D After a Drug Holiday?
Vitamin D and Calcium Reduces Fracture Risk (800IU+1200 mg/d) 2007

USPSTF: No Risk Reduction for Vitamin D and Hip Fracture- 2014

Risk of Hip Fracture by Age Group in WHI: Age and Fall Interaction

A Host of New Drug Treatments!!!
Summary

- 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”