Disclosures

- Advisory boards: Alexion, Amgen, Lilly, Merck, Radius Health

- Scientific grants: Alexion, Amgen, Immunodiagnostics, Lilly, Merck, Regeneron, Radius Health, Roche Diagnostics, Ultrageneics

- Speakers Bureaus: None

- Equity: None
HOW LONG TO TREAT?

• Usually not a question for other chronic diseases
  • Hypertension
  • Dyslipidemia
  • Diabetes
  • CHF

• For Osteoporosis: “Is not, is probably not, perhaps is not, maybe not yet; it’ll be over.....”

  Miller PD Exp Opinion Pharmacotherapy 2003
  Bonnick SL JCD 2011
  Khosla S et al JCEM 2012
  Strim O et al OI 2015
  McClung MR OI 2015
  Adler R et al JBMR 2016

I Started My Holiday One Year Ago, and I don’t know how to judge whether it’s over!

Moses and God 1313 BC
Bisphosphonate “Drug Holiday”

- 1. Not a topic of discussion when BP 1st launched (1995)
- 2. Became a consideration after July 9, 2002 (WHI JAMA publication) when BP Rx increased in younger postmenopausal women.
- 3. Became more widely discussed after FLEX (Black D et al JAMA 2006), and the better science defining BP Pharmacology became available (Russell G OI, 1970 and Bone 2010).
- 4. FRAX™ also drove the drug holiday discussion in women who, by the FRAX™ calculation had been at low risk before bisphosphonates were started.
- 5. Still, not a standard of care in the USA, though the FDA, and most other “bone” professional societies suggest considering a holiday in lower risk patients after 3-5 years of use.


September 9, 2011:
FDA Advisory Committee Hearing on Bisphosphonate Duration of Use

1. Little evidence of continual efficacy beyond 5 years
2. Safety concerns re atypical subtrochanteric femur fractures with longer term use

Is The Question:

“Is There Evidence for Efficacy Beyond 5 years?”

A Fair Question?

No study can maintain a placebo group for long periods to have robust long term fracture data between the original randomized placebo vs treatment groups

Bisphosphonate Pharmacology

Is Unique
The Pioneers of Bisphosphonates (P–C–P) Pharmacology

Bisphosphonates

- 1. Not metabolized
- 2. Retained in bone
- 3. Re-cycled
- 4. Maintain some biological activity after discontinuation

Russell G et al BONE 2011
Rat Skeleton after Single dose $^{14}\text{C}$-labeled IV Zoledronic Acid

From Green JR Personal Communication

BISPHOSPHONATE UPTAKE AND DETACHMENT FROM BONE SURFACES

Lower Affinity BP
- Less uptake
- More diffusion in bone
- High desorption
- Low reattachment

Higher Affinity BP
- More uptake
- Less diffusion in bone
- Low desorption
- High reattachment

Graham Russell et al. Osteo Int 2008; 19: 733-759
Despite the Pharmacology of Bisphosphonates

Perhaps they may not have a prolonged effect on fracture reduction in osteoporosis patients when stopped?

Miller PD JCEM 2016 (in press)

Clinical Trial Data

On which bisphosphonate “holidays” are based is based on very small patient numbers
FLEX Trial
Fosamax Long-Term Extension
A re-randomization of the original
FIT 1 and FIT 2 alendronate registration trials
6,459 from the FIT trials

1,099 of the treated groups entered FLEX

FN BMD < 0.68 gm/cm²

376 from FIT 1 (VCF)

723 from FIT 2 (No VCF)  Black D et al JAMA 2008

An Example of How Change in the Reference Database Affected FIT-FLEX
The number of patients with “osteoporosis” was cut in half

<table>
<thead>
<tr>
<th>T-score Range</th>
<th>Original Hologic Reference Values</th>
<th>NHANES III Reference Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to -1.0</td>
<td>0 (0%)</td>
<td>2 (0.1%)</td>
</tr>
<tr>
<td>-1.0 to -2.0</td>
<td>36 (0.8%)</td>
<td>1362 (30.7%)</td>
</tr>
<tr>
<td>-2.0 to -2.5</td>
<td>934 (21.1%)</td>
<td>1435 (32.4%)</td>
</tr>
<tr>
<td>Less than -2.5</td>
<td>3460 (78.1%)</td>
<td>1631 (36.8%)</td>
</tr>
</tbody>
</table>

FIT 2: Lowest FN -1.6 by Hologic
FIT 2: NHA Lowest FN -2.0

Lumbar Spine BMD Change in FLEX Population: From Beginning of FIT to Completion of FLEX

- ALN/placebo (n = 437)
- ALN/ALN (pooled 5-mg and 10-mg groups: n = 662)

Mean Percent Change From FIT Baseline, %

Age range: 69-91 yo


Total Hip BMD Change in FLEX Population: From Beginning of FIT to Completion of FLEX

- ALN/placebo (n = 437)
- ALN/ALN (pooled 5-mg and 10-mg groups: n = 662)

Mean Percent Change From FIT Baseline, %

Serum CTx: Mean Absolute Value Change From FIT and FLEX Baselines

- ALN/placebo (n = 97)
- ALN/ALN (pooled doses: n = 139)

Black D et al. JAMA 2006

Serum P1NP: Mean Absolute Value Change From FIT and FLEX Baselines

- ALN/placebo (n = 97)
- ALN/ALN (pooled 5-mg and 10-mg groups: n = 139)

P1NP = N-propeptide of type 1 collagen.
Black DM et al. JAMA 2006
**FLEX: Incidence of Fractures (prospective)**

- **Relative Risk Reduction**: 55%
- **ARR**: 2.9%
- **P**: 0.013
- **RR = 0.9**
  - **CI (0.6, 1.2)**
- **RR = 1.0**
  - **CI (0.8, 1.4)**

- **Fracture Incidence, %**
  - **ALN/PLB (n = 437)**
  - **ALN/ALN (n = 662)**

  - **Clinical Vertebral**: 5.3% (ALN/PLB), 2.4% (ALN/ALN)
  - **Vertebral Morphometric**: 11.3% (ALN/PLB), 9.8% (ALN/ALN)
  - **Nonvertebral**: 19.0% (ALN/PLB), 18.9% (ALN/ALN)

- **Time-to-First Fracture, year of FLEX**
  - **Placebo group**: some fractured; some did not
  - **Relative Risk Reduction**: 55%
  - **P**: 0.013
  - **ARR**: 2.9%

The Truth In FLEX

1. The primary analyses was a change in BMD and fracture assessment was an exploratory end-point.

2. The increase in the clinical vertebral fracture or non-vertebral risk with discontinuation of alendronate prospectively was NOT related to the level of baseline BMD nor baseline prevalent VCF in FLEX. (Table 4 in Black D et al JAMA 2006).

Interaction Between Baseline T-score or VCF and Risk Reduction

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Placebo, No. (%)</th>
<th>Alendronate, No. (%)</th>
<th>RR (95% CI)</th>
<th>Placebo, No. (%)</th>
<th>Alendronate, No. (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline BMD T-score at femoral neck</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2.0</td>
<td>461 19 (13.1) 42 (14.0)</td>
<td>1.5 (0.86-2.6)</td>
<td>3 (1.7) 4 (1.4)</td>
<td>0.64 (0.18-4.2)</td>
<td>2.0 to ≤2.0</td>
<td>311 26 (20.6) 36 (20.5)</td>
</tr>
</tbody>
</table>

P-value for interaction: 0.40

Prevalent vertebral fracture:

<table>
<thead>
<tr>
<th>No.</th>
<th>Placebo, No. (%)</th>
<th>Alendronate, No. (%)</th>
<th>RR (95% CI)</th>
<th>No.</th>
<th>Placebo, No. (%)</th>
<th>Alendronate, No. (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>723</td>
<td>48 (16.7) 51 (14.1)</td>
<td>0.66 (0.39-1.13)</td>
<td>11 (5.8) 7 (1.6)</td>
<td>0.42 (0.15-1.11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>376</td>
<td>56 (23.3) 62 (27.7)</td>
<td>1.20 (0.80-1.8)</td>
<td>12 (8.0) 9 (4.0)</td>
<td>0.47 (0.19-1.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P-value for interaction: 0.23

Black D et al JAMA 2006
Editorial NEJM

Acknowledged that in FLEX there was NO INTERACTION between either baseline BMD or prevalent VCF and the change in risk for new clinical vertebral fracture or non-vertebral fracture (prospective)

Cummings SR, Black D et al NEJM 2012

Data from FLEX and Horizon

• 1. Neither provide definitive information on fracture risk in patients who continue or discontinue treatment.

• 2. In both the effect of continued treatment was an exploratory aim, did not include the entire randomized populations, limited power to detect modest differences in fracture rates reflected in wide confidence intervals in fracture outcomes. Neither T-score or prior VCF could predict who would/would not fracture off therapy.

• 3. Fractures were only clinical vertebral (FLEX) or morphometric vertebral (HORIZON).

• 4. Non-vertebral fracture reduction in FLEX was a post-hoc analysis

Boonen S et al JBMR 2012
Think, Don’t Just Accept Dogma/Status Quo

“Only doubt is certain and disbelief worth believing. Without this courage there can be no learning. Believe nothing.”

Anonymous

Osteoporosis Drug Holidays
A Re-Thinking of the Data

Perhaps we should not stop anyone with “low” BMD, prior fractures or older (69+)

And.....

BMD changes or BTM may (or may not) be useful in deciding when a holiday is over
• "...no data to truly support that restricting the duration of use was beneficial for patients requiring long-term bisphosphonate treatment for osteoporosis"

• "...the committee was not confident that implementing a drug holiday or discontinuing bisphosphonate use after a period time would be beneficial"

• "... the committee recommended that the label should further clarify the duration of use for bisphosphonates”

• The committee members who voted “No” (17-6) noted that the labeling does not need further clarification at this time and that it should only include information that is known since there is a lack of data on the benefit versus risk of limiting the duration of use of bisphosphonates.


• Decisions to continue treatment must be based on individual assessment of risks and benefits and on patient preference

• Patients at low risk for fracture (e.g., younger patients without a fracture history and with BMD approaching normal) may prove to be good candidates for discontinuation of bisphosphonate therapy after 3 to 5 years

• Patients at increased risk for fracture (e.g., older patients with a history of fracture and BMD remaining in the osteoporotic range) may benefit further from continued bisphosphonate therapy

Is The Trend to Stop a BP  
An uncertain trend?

Why Not a Holiday for Other Osteoporosis Drugs?
Effect of Discontinuation of Denosumab on LS and TH BMD

Miller PD et al. Bone. 2008;43:222-229

Effect of Discontinuation of Denosumab on sCTX and BSAP Levels

Miller PD et al. Bone. 2008;43:222-229
Where Are We in 2016?

Should Drug Holidays Be Considered? (or Reevaluated)?

- YES (to which question)?

- But consider ONLY in lower risk patients:
  - no prior fracture, T-scores > -2.0, and younger age (<65 years)
  - and........
  - Because we have no data on patients with steroid use, stage 3-5 CKD, diabetes mellitus and other diseases that increase fall risk (Parkinsons, MS, etc) one must use caution and clinical judgement in any patient not “fitting” the strict randomization criteria of FIT/FLEX
Treat the Person, Not Just Their Bones

“The good physician treats the disease; the great physician treats the patient who has the disease.”

Sir William Osler

Why Are Osteoporosis Pharmacological Treatments Declining? Confusion and.........
FEAR

ASBMR Reports on Atypical Femoral Fractures

- Shane E et al JBMR 2010
- Shane E et al JBMR 2014

No Causality Established
AFFs Occur in Nonusers …

- ASBMR, 2010: “It is also important to note that atypical fractures have been reported in patients who have not been exposed to BPs.”

- ASBMR 2014: “Every study included AFF patients unexposed to BPs.”

… and AFFs Look the Same in Nonusers

How Uncontrolled Case Series

May Lead to Beliefs

The epidemiological data (retrospective) associating bisphosphonates with ASFF are mostly uncontrolled and NONE have controlled for baseline BMD
Confounded by Indication

The very patients who are more likely to receive bisphosphonates (low bone mass) are the ones that have a higher risk for all forms of femur fractures, including sub-trochanteric.

Authors Acknowledge Confounding

“The increased risks of femur fracture, irrespective of fracture location, that were associated with bisphosphonate use are probably the consequence of osteoporosis.”
## Different Results With Different Definitions

<table>
<thead>
<tr>
<th>Criteria</th>
<th>2011 Schilcher</th>
<th>2013 Schilcher</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total # of AFFs</td>
<td>59</td>
<td>80</td>
</tr>
<tr>
<td>AFFs w/ BP Use</td>
<td>46 (78%)</td>
<td>49 (61%)</td>
</tr>
<tr>
<td>AFFs w/ No BP Use</td>
<td>13 (22%)</td>
<td>31 (39%)</td>
</tr>
<tr>
<td>Total # of Subtroch/Shaft</td>
<td>322</td>
<td>277</td>
</tr>
<tr>
<td>Subtroch/Shaft w/ BP Use</td>
<td>72 (22%)</td>
<td>69 (25%)</td>
</tr>
<tr>
<td>Subtroch/Shaft w/ No BP Use</td>
<td>250 (78%)</td>
<td>208 (75%)</td>
</tr>
</tbody>
</table>

2011 Schilcher NEJM; 2013 Schilcher Bone

## FDA “Duration of Use” Hearing

Based on the assumption that risk of ASFF is related to duration of use
Bisphosphonate-Associated Atypical Femur Fractures Are Associated with Duration of Use

Incidence of atypical femur fractures according to duration of bisphosphonate exposure (unadjusted and age-adjusted, showing incidence and 95% confidence intervals)

True incident rate should have, as the denominator, the number of patient year exposure (total cohort, total exposure) rather than duration of BP exposure. Dell’s paper is NOT a true incident rate.

Dell R et al JBMR 2012

Incidence Rate Calculation

- The Dell et al description of how they calculated the incidence rate is not quite right. The paper says that the denominator was the person-time contributed by persons in the cohort over the 5-year study period.

- This limitation is important b/c the failure or inability to use patient-years of BP use for the denominator inhibits Dell’s data from being a true incidence rate calculation, and then of course the duration of use analysis included gaps in BP prescriptions, so those numbers may well be off as well.

Holidays

• 1. Limitation of use predicated on the unique pharmacology of BP’s and the assumption that any “persistent” effect on BMD or turnover translates into persistent effect on fractures.

• 2. The limitation of duration of use is predicated on the belief that ASFF risk increased with the increase duration of BP use.

• 3. FLEX actually dismisses the 1st theory-BMD change and BTM change in FLEX in those off therapy did not predict more or less fractures in those on holidays; nor did the baseline BMD or prevalent VCF predict who might vs who might not develop a fracture on holiday.

• 4. All epidemiological reports on BP-associated ASFF are confounded by indication.

So, What’s The Take-home Message?

Holidays from osteoporosis therapies have poor evidence for justifying a “drug break”.

Treat the patient and continuously treat the high risk patient

(older, osteopenic without prevalent VCF)