Controversies in Long Term Osteoporosis Treatment

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Bisphosphonates (and other Treatments) Reduce Fracture Risk up to 5 Years


Benefits vs. Risk, 10,000 women treated 3 years

<table>
<thead>
<tr>
<th>Fractures prevented</th>
<th>RR for AFF</th>
<th>AFF caused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>112</td>
<td>1.7</td>
</tr>
<tr>
<td>Spine</td>
<td>545</td>
<td>0.1</td>
</tr>
<tr>
<td>Non-vertebral</td>
<td>164</td>
<td></td>
</tr>
<tr>
<td></td>
<td>822</td>
<td>19 (worst case)</td>
</tr>
</tbody>
</table>
BP treatment for up to 5 years: the Bottom Line

Benefits for BP treatment (for 3-5 years) far outweigh any risks, even allowing for some risk of AFF.

What about treatment beyond 5 years?

### Treatment Beyond 5 Years

**Bisphosphonates**
- Alendronate and Zol
- Other BPs
- Denosumab

### Osteoporosis Treatment Long-term Randomized Extension Studies for Alendronate and ZOL

<table>
<thead>
<tr>
<th></th>
<th>Zoledronic acid</th>
<th>Alendronate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIT</strong></td>
<td>ZOL (n = 3889)</td>
<td>ALN (n = 3236)</td>
</tr>
<tr>
<td><strong>RCT – EXT1</strong></td>
<td>ZOL (n = 330)</td>
<td>ALN 5 mg (n = 333)</td>
</tr>
<tr>
<td><strong>RCT – EXT2</strong></td>
<td>ZOL (n = 350)</td>
<td>ALN 10 mg (n = 332)</td>
</tr>
</tbody>
</table>

**Design of the FIT Long-Term Extension (to 10 years) of Alendronate (FLEX)**

- Mean ALN use: 5 years
- FLEX (5 yrs)
- BMD: Primary endpoint
- Fractures: Exploratory endpoint


### Other Studies

- HORIZON-PFT 1
- RCT – EXT 2
- VERT-MN 7
- RCT – EXT 8
- OL-EXT 9

**Black DM, et al.**
- J Bone Miner Res. 2012; 27:243-254
- JAMA. 1996;348:1535-1541
- JAMA. 2006;296:2927-2938
- Osteoporos Int. 2000;11:83–91
- Bone. 2003;32:120-126
- Calif Tissue Int. 2004;75:462-468
- JAMA. 2007;356:1809-1822
- J Bone Miner Res. 2012; 27:243-254
- ASBMR 2013 (abstract no. SA0389)
- JAMA. 2006;296:2927-2938
FLEX: Alendronate
Randomized, Double-blind Treatment
5 years of ALN followed by 5 more years or PBO

<table>
<thead>
<tr>
<th>Fractures</th>
<th>Placebo, No. (%) (n=427)</th>
<th>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</td>
<td>23 (5.3)</td>
<td>16 (2.4)</td>
<td>0.45 (0.24–0.85)</td>
</tr>
<tr>
<td>Morphometric</td>
<td>46 (11.3)</td>
<td>60 (9.8)</td>
<td>0.86 (0.60–1.22)</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonspine</td>
<td>83 (19.0)</td>
<td>125 (18.9)</td>
<td>1.00 (0.76–1.32)</td>
</tr>
<tr>
<td>Hip</td>
<td>13 (3.0)</td>
<td>20 (3.0)</td>
<td>1.02 (0.51–2.10)</td>
</tr>
</tbody>
</table>

Reductions (RR) for fractures for continuing bisphosphonates: Alendronate and ZOL

<table>
<thead>
<tr>
<th>Fractures</th>
<th>Alendronate FLEX: 5 yrs/5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Hazard (± 95% CI)</td>
<td>1.00 (0.8, 1.3)</td>
</tr>
</tbody>
</table>

Vertebral FX (clinical)

0.45 (0.2, 0.85)

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

Black JAMA 2006; Black et al. JBMW 2012

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

Dell et al. JBMR 12/12

Do Atypical Femur Fractures Increase with Duration of Treatment? Recent Danish Cohort (81,000 users)*

Abrahamsen, et al BMJ 6-16

Is AFF incidence increased with longer duration of use?

I HEARD THE JURY IS STILL OUT ON...

Risks of long term osteo therapy

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
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
  o NEJM; 5/2012
    - Perspective from FDA together with an analysis from FLEX
  o Consider femoral neck BMD and vertebral fracture status at the end of the initial treatment period

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:
  o Women with femoral neck BMD T-score <-2.5
  o In women with existing vertebral fractures, continue treatment in those with fn BMD T-score <-2.0
  o Others can discontinue with retention of some benefits for up to 5 years

Other factors relevant to deciding to discontinue after 5 years

- BMD and vertebral fracture status at time on discontinuation
- *Bone markers not useful
- Perhaps other factors such as age and fracture on treatment

\*Bauer, et al. JAMA (5/14)
Overview for long-term use of alendronate and ZOL

- Some residual benefits after stopping for alendronate and zoledronic acid
- Reductions in spine fractures
- Benefits of long-term use are smaller than benefits for short-term use
- On the other hand, risks might be increasing over time
- Risk benefit ratio for long term continuation not as favorable as for short-term use

Summary of benefits vs. risks for ALN or ZOL treatment as a function of time

<table>
<thead>
<tr>
<th>Treatment 3-5 years</th>
<th>Treatment Beyond 5 yrs</th>
<th>Treatment Beyond 10 yrs with ALN (6 years with ZOL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefits: Hip, non-vertebral and spine reductions</td>
<td>Benefits: Only spine reductions</td>
<td>Benefits unproven</td>
</tr>
<tr>
<td>Risks</td>
<td>Risks</td>
<td>Risks uncertain</td>
</tr>
</tbody>
</table>

Long-term use of other bisphosphonates

- Limited data for Risedronate and Ibandronate on long term use
- Long term continuation seems to continue lowered fracture risk (similar to ALN and ZOL)
- BUT discontinuation likely results in faster loss of benefits of therapy
  - Different pharmacologic characteristics
- For Risedronate and Ibandronate, after discontinuation, cannot assume same on-going benefits as seen with ALN and ZOL

Long-term use of non-bisphosphonate therapies

- For Teriparatide, Denosumab, Raloxifene, HRT, benefits are rapidly lost after discontinuation
- Very different from Alendronate and Zoledronic acid
- Need to be continued long-term or switched to another therapy after discontinuation
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)

Thanks!