How long to treat?

11th Annual Update on Osteoporosis and Skeletal Health
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E. Michael Lewecki, MD
New Mexico Clinical Research & Osteoporosis Center
University of New Mexico School of Medicine
Albuquerque, NM

Conclusions

• Start treatment when benefits >> risks
• Continue treatment when benefits >> risks
• Only one osteoporosis drug has a time limit: teriparatide is not recommended for more than 24 months lifetime use
• Drug holidays apply only to bisphosphonates for some patients under some circumstances, with different considerations for different bisphosphonates

What is the real problem?

• It is NOT that far too many people are being treated too long
• Rather, it is that people who need treatment are not getting it

Treatment Gap

Review of US insurance claims data (commercial + Medicare) on 98287 patients hospitalized with hip fracture, 2002-2011

Disclosure

Institutional Grant / Research Support
Amgen, Eli Lilly, Merck
Consulting / Speaking
Amgen, Eli Lilly, Merck, Radius Health, Shire, Alexion

Percent of Women Tested

DXA Office Providers

Reimbursement Rates
Myth, Reality, Uncertainty

**WARNING**

Little evidence
Many opinions

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**Myth**

Osteoporosis Drugs
Don't Work After 5 Years

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Prescriptions
The Business of Health Care

September 7, 2011, 2:52 pm | 2 Comments

F.D.A. Staff: 5 Years May Be Enough for Bone Drugs
by Duffy Wilson

Most women who take bone-building drugs like Fosamax can safely stop taking them after five years, the Food and Drug Administration said Wednesday in a staff report leading up to a broad safety review scheduled Friday by two scientific advisory committees.

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"Why Osteoporosis Drugs Don't Work"

By Dannie · October 5, 2009 at 3:30 pm - 2 replies

I was taking Forteo at least 5 years ago. My dentist did not blame the Forteo for my dental problems; he blamed the Rogert I.V.'s. I was taking Forteo when I was going on the assumption that my doctor knows best and I should follow his instructions religiously. My husband is now coaching me on how to be responsible for my health. (Dr. Whittaker and Eirina advocate our becoming responsible for our health.) I research everything that is recommended to me. It is up to me to make the right decisions about my health. To do that, I must be well informed. This steno is working much better for me.
Myth: Osteoporosis Drugs Don’t Work After 5 Years

- Reality: The evidence supports anti-fracture efficacy for as long as 10 years in appropriately selected patients
- Uncertainty
  - RCTs with a placebo group are usually 3 years for osteoporosis drugs
  - No data beyond 10 years

Studies with other drugs for chronic diseases are often far shorter, and we typically don’t know the long-term effects of any drugs for any disease.

FLEX: Fracture Intervention Trial Long-Term Extension

- Objective: Compare effects of continuing or stopping ALN after 5 years of therapy in FIT
- Primary endpoint: Hip BMD
- Secondary endpoints: BMD at other skeletal sites, BTMs
- Exploratory endpoints: fractures, histomorphometry (18 bone biopsies; 9 PBO, 9 ALN)
- 1099 subjects randomized to...
  - PBO (n = 437)
  - ALN 5 mg/day (n = 329) or ALN 10 mg/day (n = 333)
- Modified ITT using pooled data from both ALN groups for primary analyses

<table>
<thead>
<tr>
<th>Time to First Fracture, year of FLEX</th>
<th>Cumulative Incidence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALN/placebo</td>
<td>5.3%</td>
</tr>
<tr>
<td>ALN/ALN (pooled)</td>
<td>2.4%</td>
</tr>
<tr>
<td>Relative Risk Reduction 25%</td>
<td>0.013</td>
</tr>
<tr>
<td>ARR = absolute risk reduction</td>
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</tbody>
</table>

ALN = alendronate
ARR = absolute risk reduction
Continuing ALN Beyond 5 Years
Reduced NVF Risk in High Risk Women

- Post hoc analysis of FLEX data
- In women with FN T-score ≤ -2.5 after 5 years ALN and no prevalent VF, continuing ALN for an additional 5 years reduced NVF risk compared with stopping ALN
  - RR 0.50 (95% CI 0.26-0.96), P = 0.019


Hip Fracture Risk Increased with Stopping Bisphosphonate Therapy

- Review of administrative claims databases in 9,063 women age 60-78 compliant with ALN or RIS at 2 years (MPR ≥ 66%) compared with those who stopped
- Hip fracture incidence was 4.76/1000 in those who continued vs 8.43/1000 in those who stopped (P = 0.016)
- Conclusion: Discontinuation of bisphosphonate therapy after 2 years may not be appropriate in this population


VERT-NA Extension: Decrease in BMD and Increase in NTX with Stopping RIS


Radiographic VF's Remain Reduced 1 Year after Stopping 3 Years of RIS


HORIZON PFT Extension Study

- Extension of original 3-year trial of zoledronic acid versus placebo
- Patients who received 3 years of ZOL were re-randomized to continue ZOL for a total of 6 years or change to placebo for the final 3 years
- Primary endpoint was FN BMD % change from year 3 to year 6
- Secondary endpoints included BMD at other skeletal sites, BTMs, and fractures


Decrease in FN BMD with Stopping ZOL

More Radiographic VF\(\text{s}\) with Stopping ZOL

Antiresorptive and BMD Effects Persist for 5 Years after Single Dose ZOL

Low Rate of VF\(\text{s}\) with 8 Years of Continuous Dmab in FREEDOM Extension

Low Rate of NVF\(\text{s}\) with 8 Years of Continuous Dmab in FREEDOM Extension

Myth

Osteoporosis Drugs Are Dangerous
Myth: Osteoporosis Drugs are Dangerous

- Reality: There are risks with any treatment, but in appropriately selected patients, the benefits of osteoporosis drugs far outweigh the risks
  - RCTs, FDA review and approval

- Uncertainty
  - Rare adverse effects of drugs may not be apparent in RCTs
  - Causality is difficult to determine with sporadic case reports of patients in clinical practice

Perpetuation of this myth is fueled by media reports that are typically factually correct but often lacking in balance and...

Bisphosphonate Safety Issues

**Side Effects**
- Short-term
  - GI distress
  - Acute phase reaction
  - Hypocalcemia
  - Renal toxicity
- Long-term
  - Osteonecrosis of the jaw
  - Atypical femur fractures
- Questionable
  - Chronic musculoskeletal pain
  - Atrial fibrillation
  - Esophageal cancer
  - Impaired fracture healing

**Side Benefits**
- Improved implant survival
- Risk of breast cancer
- Risk of colorectal cancer
- Risk of stroke
- Risk of gastric cancer
- Risk of MI in RA patients
- Risk of type 2 DM
- Mortality

Kontantinos A et al. J Clin Endocrinol Metab. 2015;100:1933-1940.
Atypical Femur Fractures

### Comparing Risks

<table>
<thead>
<tr>
<th>Incidence Rate per 100,000 Person-Years</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Hip Study (Age 70-79)</td>
<td>RIS</td>
</tr>
<tr>
<td>AFF 4-5 Years BP</td>
<td>RIS</td>
</tr>
<tr>
<td>AFF 6-8 Years BP</td>
<td>RIS</td>
</tr>
<tr>
<td>AFF 8-10 Years BP</td>
<td>RIS</td>
</tr>
</tbody>
</table>

Half-Myth: Drugs Don’t Work If Patients Don’t Take Them

- **Reality**
  - Most drugs stop working as soon as patients stop taking them
  - Bisphosphonates are an exception: slow offset of effect

- **Uncertainty**
  - Limited data on duration of anti-fracture effect after stopping osteoporosis medication

### LS BMD Slowly Decreases After Stopping Alendronate (vs. HT)

- **Bisphosphonates Are Not All The Same**
  - Common to all N-containing bisphosphonates:
    - Poor oral bioavailability ~0.5%
    - ~50% attaches to bone, ~50% excreted by kidneys unmetabolized
  - Affinity for bone: ZOL > ALN > IBN > RIS
  - Long skeletal half-life
  - Longer effect after discontinuation with higher affinity?
  - Implications for drug holidays?
  - Antiresorptive potency: ZOL > RIS > IBN > ALN
  - Inhibition of FPPS
  - Faster onset of effect with greater potency?
  - Greater fracture risk reduction with greater potency?
  - Greater risk for osteoporosis with greater potency?

Drugs Don’t Work If Patients Don’t Take Them

- Reality
  - Most drugs stop working as soon as patients stop taking them
  - Bisphosphonates are an exception: slow offset of effect

- Uncertainty
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Drug Holiday

• Elective temporary withholding of bisphosphonate after at least 3-5 years in appropriate patients
  – NOT “drug retirement”
  – NOT “stopping treatment”
  – NOT for non-bisphosphonates
• Rationale: persistence of anti-fracture benefit while possibly reducing long-term risks
  • Very little data, many opinions
  • Periodic reevaluation of balance of benefits and risks

Rationale: persistence of anti-fracture benefit while possibly reducing long-term risks

Very little data, many opinions

Periodic reevaluation of balance of benefits and risks


• "... 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"


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

Patients with FN T-score < -2.5 after 3 to 5 years of bisphosphonate treatment and those with vertebral fracture and T-score ≤ -2.0 may benefit from continuing therapy

Patients with FN T-score > -2.0 are unlikely to benefit from continued therapy

FDA Perspective


Response to FDA Perspective


Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research

Robert A. Adler 1,*, Ghaba Ehrs, Kyle, Thomas 2, Douglas C. Bauer 1, Sarah M. Cane 1, Robert L. Clark 1, Gregory A. Colley 1, Juliette Consten 1, Matthew T. Drakes 1, Beatrice J. Edwards 1, Murray J. Evans 1, Susan I. Greenston 1, Ross McKinnon J.A., Robert J. Pignolo 1, and Deborah E. Sellmayer 1

Is T-score > -2.5 a treatment target?

More later

Drug Holiday Principles

• Optimal duration of use has not been determined
• No time limit on bisphosphonate treatment has been established
• No standard of care
• Periodically evaluate balance of benefit and risk
• Stop treatment when it should not have been started in the first place

Starting a Drug Holiday

• Oral bisphosphonates
  – Consider drug holiday after 3 to 5 years of treatment if fracture risk is no longer high (T-score > -2.0, no major fracture)
  – After 10 years of treatment, consider drug holiday or switch to another agent (milder antiresorptive or anabolic drug) even when fracture risk remains high
• Zoledronic acid
  – Extend dosing interval after 3 years of treatment if fracture risk no longer high
  – Extend dosing interval or switch to another agent after 6 years of treatment even if fracture risk remains high

Strategies for Ending a Drug Holiday

• After 1 to 2 years off treatment, make treatment decisions as if patient were treatment naïve (use treatment guidelines)
• End drug holiday when BMD decreases (T-score ≤ -2.5), BTM increases, or incident major fracture occurs
• Establish an arbitrary time to end the drug holiday when starting it

Rapid BMD Decrease with Discontinuation of Denosumab

What to do after long-term Dmab and fracture risk is no longer high?

A little data . . .
Long-term Dmab / Fx Risk Not High

• Nothing is not a good option
• Lengthen dosing interval?
• Switch to mild antiresorptive?
• Switch to ZOL? ✓

Summary

• No standard of care for duration of bisphosphonate therapy
• Drug holiday may be appropriate for some patients on bisphosphonates
• Consider balance of benefits and risks
• Treatment decisions should be individualized