CONTROVERSY IN LONG-TERM CARE OF THE PATIENT WITH OSTEOPOROSIS

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Elizabeth Shane, M.D.
Professor of Medicine
Columbia University Medical Center,
New York, NY

OSTEOPOROSIS MEDICATIONS

ANTIRESORPTIVE
• Bisphosphonates
  • RANK Ligand inhibitors (Denosumab)
  • Selective Estrogen Receptor Modulators (SERMs)
  • Calcitonin
  • Hormone therapy
  • Cathepsin K inhibitors

ANABOLIC
• Parathyroid hormone analogs
• Sclerostin inhibitors

Disclosures

• Industry Research Support (To Institution)
  – Amgen
  – Eli Lilly
• Consultancies, Speakers Bureaus, Financial holdings
  – Radius Pharmaceuticals
• Discussion of unlabeled use of drugs
  – None

Bisphosphonates (BPs) have dominated the therapy of osteoporosis for the last 2 decades.

• What are their benefits?
• What are their side effects and complications?
  – Osteonecrosis of the Jaw, Atypical Femur Fractures
• How long should we treat to maximize benefit and minimize risk?
• Which patients can safely stop and which should continue?
### Bisphosphonates Available in the US

- **Alendronate (Fosamax)**
  - Oral weekly
- **Zoledronate (Reclast)**
  - IV annually
- **Risedronate (Actonel, Altelvia)**
  - Oral weekly, monthly
- **Ibandronate (Boniva)**
  - Oral daily, monthly
  - IV every 3 months

### Bisphosphonates Have Long Half-Life

- “The gift that keeps on giving”
- Long residence in bone with release and possibly recycling of drug
- Sufficient drug retained so that benefit continues after therapy is stopped
- Half-life estimated in years – but differs for different bisphosphonates
  - Longer for alendronate and zoledronic acid
  - Shorter for risedronate, ibandronate and pamidronate

### EXPECTED Benefits of Bisphosphonates

**Bisphosphonates for Postmenopausal Osteoporosis**

- BPs increase bone mineral density
  - At the spine by 5-8%
  - At the hip by 3-5%
- In multiple, high quality RCTs, they reduce
  - Vertebral fractures by 40-77%
  - Hip fractures by 40-60%
  - Non-vertebral fractures by 30-40%
- Reduction in fracture risk
  - Sustained when continued beyond 5 years
- In randomized clinical trials, very safe

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**UNEXPECTED Benefits of Bisphosphonates**

**Bisphosphonates Associated with LOWER MORTALITY**
- After hip fracture \(^1,2,3\)
- In community-dwelling elderly \(^4\)
- In institutionalized elderly \(^5\)


**Bisphosphonates Associated with Decreased Risk of Cancer**
- Breast cancer \(^1-5\)
- Colon cancer \(^6,7\)
- Gastric cancer \(^8\)


**Risks of Bisphosphonates**
Osteonecrosis of the Jaw (ONJ)

AKA Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ)

In 2014, renamed Medication-Related Osteonecrosis of the Jaw (MRONJ)

Updated AAOMS Case Definition of ONJ

• Current or previous treatment with antiresorptive or antiangiogenic drugs
• Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxilla or mandible
• No history of craniofacial radiation and no obvious jaw bone metastases
• No healing after 8 weeks

Osteonecrosis of the Jaw

• Reported with all BPs 1 and denosumab (Prolia) 2-4
  • and angiogenic agents
• >90% of cases occur in cancer patients on long-term, high dose IV BPs for prevention of skeletal-related events
  • Incidence 1-16% 1
• Very rare in patients on bisphosphonates for osteoporosis 5-11
  • 1-10/10,000 5,6
  • 0.4/10,000 7
  • 1/250,000 8

Risk Factors for ONJ

• Dental extraction or surgery
• Poorly fitting dentures
• Periodontal disease
• Potency of antiresorptive drug
  • Denosumab = Zoledronic acid > Pamidronate >>>> Alendronate, Risedronate, Ibandronate
• Long duration of BP use - >3-4 yrs

References:
2. Stopeck et al., J Clin Oncol 2010
3. Henry et al., J Clin Oncol 2011
4. Fizazi et al., Lancet 2011
7. Malden et al., J Bone Miner Metab, 2012
8. Felsenberg et al., Deutsches Arzteblatt, 2006
10. Hellstein et al., JADA, 2011
11. AAOMS Position paper 2014

Prevalence of ONJ in Patients on Oral BPs by Duration of Use

21 per 10,000 at ≥ 4 yrs

2011 Position Statement: American Dental Association *

Benefits of osteoporosis therapy outweigh low risk of developing ONJ

*Hellstein et al., Managing the care of patients receiving antiresorptive therapy for prevention and treatment of osteoporosis. JADA.org, 10/31/2011

Atypical Femur Fractures

TYPICAL (Ordinary) Hip Fractures

Femoral Neck (FN) Fracture
Intertrochanteric (IT) Fracture

BPs reduce these types of fractures by 40-60%

TYPICAL and Atypical ST/FS Fractures

Typical **SPIRAL** Subtrochanteric Fracture

**COMPLETE** Atypical **TRANSVERSE** Subtrochanteric Fracture

Courtesy of Eve Donnelly, PhD

**Incomplete** Atypical Femur Fracture

Plain X-rays

Bone Scan

MRI

Even DXA

Courtesy of Fergus McKiernan, MD

Risk Factors for Atypical Femur Fractures

- Younger age
- Obesity
- Asian race 1,2,3
- Hispanic ethnicity 3
- Low vitamin D levels, low serum calcium levels
- Multiple antiresorptive drugs
- Glucocorticoids
- Rheumatoid arthritis
- Diabetes
- **Long duration of BP use – usually > 5 yrs**

1. Lo et al., Bone 2012;51:181-4
2. Dell et al., JBMR 2012; 27:2544-50
3. Mariano et al., Cite Orthop Trau Res eipub Oct 29, 2013

Are atypical fractures associated with bisphosphonate use?

Most Studies **WITH** Radiograph Review Suggest They Are.
Swiss Case-Control Study
Meier et al., Arch Intern Med 2012

- 477 patients > age 50 admitted with ST or FS fractures 1999-2010
- 438 had classic fractures and 6% used BPs
- 39 had atypical fractures and 82% used BPs

Adjusted OR for BP use - 69.1
95% CI 22.8-209.5

Atypical Fractures per 100,000 BP-exposed Patients by Duration of Use - Kaiser Permanente

The RELATIVE RISK of a patient with an AFF being on BP therapy is HIGH.

However, The ABSOLUTE RISK of AFFs in Patients on Bisphosphonates is VERY LOW.

1. Meier et al., Arch Intern Med 2012
3. Feldstein et al., J Bone Miner Res 2012
The Kaiser California Study

- 4 years of BP use, risk of AFF
  - 30 per 100,000 patient years
- 10 years of BP use, risk of AFF
  - 125 per 100,000 patient years

White US women age 65 with T-score -2.5 and no risk factors:

Risk of classic hip fracture - 280 per 100,000 patient yrs
Other osteoporotic fractures - 1,200 per 100,000 patient yrs

Shane et al., J Bone Miner Res 2010

Important Clinical Features of AFFs

- Stress or insufficiency fractures
- 75% have prodromal pain
- 25-50% are bilateral
  - often located at same level in the opposite femur

Dell et al., J Bone Miner Res 2012

Proposed Pathogenetic Mechanisms for Antiresorptive Therapy and Atypical Femur Fractures

Prolonged suppression of bone turnover may adversely affect bone material

Likely applies to both Bisphosphonates and Denosumab

Prevent healing of stress fractures.


AFF Risk Declines After Stopping BPs

- Swedish case-control study
  - 59 cases, 269 matched controls
- Most AFFs occurred within 1 yr of last BP Rx
- 70% risk reduction for every yr since last use
  - Adjusted OR 0.28 (95% CI 0.21, 0.38)
- Risk reduction similar for those taking BPs for < or > 2 yrs
ONJ and Atypical Femur Fractures: Summary

- Strongly associated with BP therapy, though BPs not proven to be causal
- Directly related to duration of BP treatment
- ONJ is extremely rare in patients treated with the doses of BPs used for osteoporosis — basically a NON-ISSUE
- Atypical Femur Fractures are a greater concern — unusual before 5 years of use

Long-term Side Effects of BPs: Influence on Management of Osteoporosis

Recognition of Long Term Risks Has Influenced How We Treat Osteoporosis

- Avoid bisphosphonates and denosumab in patients at low risk of fracture
- Avoid combination anti-resorptive therapies — e.g., estrogen + BPs, SERMs + BPs, denosumab + BPs
- As 75% of patients with AFFs have prodromal pain — Ask patients about thigh or groin pain — Image patients with unexplained thigh or groin pain
- Reassess patients after 3-5 years of BP treatment and consider drug holiday where appropriate

How Long To Treat Osteoporosis With Bisphosphonates?

- The concept of a drug holiday
- Very controversial, though has become more generally accepted over time
- But for whom is it appropriate?
- How long should it last?
Bisphosphonate Long-term Efficacy Analysis Predominantly Based Upon

- ALENDRONATE – FIT and FLEX data
- ZOLEDRONIC ACID – HORIZON and HORIZON EXTENSION

FIT Long-Term Extension of Alendronate (FLEX)*

Primary endpoint: Change in hip BMD

FIT (3 to 4.5 yrs)
Placebo N = 3,223
Alendronate N = 3,236

Randomized in FLEX
N = 1,099

Post-FIT (1-2 yrs)
Placebo N = 437
Alendronate, 5 mg N = 329
Alendronate, 10 mg N = 333

40% 30% 30%

Zeledronic Acid HORIZON Extension Study

Primary endpoint: Change in hip BMD

N = 7,736

Placebo: N = 3,876
Zoledronate 5 mg IV for 3 years: N = 3,867

Randomized in Extension
N = 1,233

EXTENSION STUDIES: Key Limitations

- Not powered for fracture outcomes
- Looked only at efficacy (for vertebral fractures)
  - No analysis of benefits versus risks
- Included only femoral neck BMD
Predictors of Vertebral and Non-vertebral Fractures OFF Therapy

- **Age**
  - ~50% increase for any clinical fracture per 5 year increase
  - in FLEX but not HORIZON
- **Fem Neck or Total Hip T score ≤ -2.5**
  - CLINICAL Vert FX risk: FLEX 2-fold increase
  - MORPHOMETRIC Vert FX risk: HORIZON 3-4 fold increase
- **Incident fractures during core HORIZON trial**
  - Morphometric Vert FX ~ 5-fold increase in Morphometric Vert FX
  - Non-vert FX ~ 2-fold increase in incident Non-vert FX
- **Having more risk factors increased fracture risk (HORIZON)**
  - Low T score, prevalent fracture, incident fracture

UCSF Opinion on BP Continuation
(Black et al., New Engl J Med 2012)

- No consistent reduction in non-vertebral fractures
- Reasonably consistent ~52-55% reduction in vertebral fractures
- Therefore, base recommendations on reductions in vertebral fracture risk
- Those at higher absolute risk will have larger benefit
  - *Lower "Number Needed to Treat" (NNT)*
- Use hip BMD and other risk factors to define groups at higher absolute vertebral fracture risk
  - *Hip BMD related to vertebral fracture risk in FLEX and HORIZON*
### UCSF Analysis Summary:
Groups at High Absolute Risk of Fracture May Benefit From Continued Therapy After 5 Years

**After 5 years of alendronate or 3 years of zoledronate:**
- Many women can discontinue with little loss of efficacy
- Those at higher risk of vertebral fracture may benefit from continuing
  - FN BMD T-score below -2.5 - NNT 21
  - Prevalent vertebral fractures and somewhat higher FN BMD T-score (up to -2.0) - NNT 17
- Cannot generalize to risedronate or ibandronate

### How Long to Treat with Bisphosphonates?

- 3-5 years appears to be safe for most patients
- After 3 years of Zoledronate or 5 years of Alendronate, assess for ongoing fracture risk
  - Clinical assessment (Fx history), DXA, Vertebral Fracture Assessment

<table>
<thead>
<tr>
<th>Lower Risk</th>
<th>Higher Risk</th>
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<tbody>
<tr>
<td>Drug Holiday After 3-5 years</td>
<td>Drug Holiday After 10 years</td>
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### My Approach to Long-term Management of Postmenopausal Osteoporosis

**LOW Risk Women**
- Treat with oral BPs for >5 yrs, IV BPs for >3 yrs
- Reevaluate

<table>
<thead>
<tr>
<th>Lower Risk</th>
<th>Higher Risk</th>
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<tr>
<td>BMD ≥ -2.0 at hip and spine</td>
<td>BMD ≤ -2.5 at FN or TH</td>
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<tr>
<td>No incident fractures on Rx</td>
<td>Hip BMD between -2.5 &amp; -2.0 BUT ≤ -2.5 at spine</td>
</tr>
<tr>
<td>No prevalent vertebral fractures</td>
<td>Prevalent vertebral fracture</td>
</tr>
<tr>
<td>Relative youth ≤ 70</td>
<td>Incident fractures on Rx</td>
</tr>
<tr>
<td>No other major risk factors</td>
<td>Older age ≥ 75</td>
</tr>
<tr>
<td>GCs, aromatase inhibitors</td>
<td>Other major risk factors GCs, aromatase inhibitors</td>
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**HIGH Risk Women**
- Drug Holiday
- Reassess every 2-3 years
- Reassessment includes
  - Clinical evaluation
  - DXA
  - +/- Bone markers (Serum CTx)
My Approach to Long-term Management of HIGH Risk Women

Treat with oral BPs for ≥5 yrs, IV BPs for >3 yrs

- Continue antiresorptive Rx for up to 10 yrs
- ....or........
- Consider alternative Rx (Teriparatide)
- Reassess every 2-3 years
  - Earlier if fracture or other high risk situation associated with rapid bone loss
- Reassessment includes
  - Clinical evaluation
  - DXA
  - +/- Bone markers (Serum CTx)

10-Year Probabilities

FRAX 10-year probability of major osteoporotic fracture for untreated 72 year-old woman with FNI-score of -3.0 is 25%

For patients in whom antiresorptive therapy is indicated because they are at high risk of fracture, the benefits of treating virtually always outweigh the risks.

Thank you!