Update in Osteoporosis: 2010

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  – Amgen
  – Roche
  – Glaxo-Smith-Kline

Topics

• Are vertebroplasty/kyphoplasty safe and effective
  – Who should receive them
• Is generic alendronate as safe and effective as Fosamax ?
• ONJ and Subtrochanteric femoral fractures with bisphosphonates
• Should patients on bisphosphonates for 5 years or more be given a drug holiday ?
Topics

- Is it safe to use bisphosphonates or rPTH with abnormal renal function?
- New Guidelines and Treatments for Glucocorticoid-induced osteoporosis?
- Where will denosumab fit into the therapeutic paradigm?
- Emerging therapies for osteoporosis?

Are vertebroplasty/kyphoplasty safe and effective

Original Article
A Randomized Trial of Vertebroplasty for Painful Osteoporotic Vertebral Fractures

Rachelle Buchbinder, Ph.D., Richard H. Osborne, Ph.D., Peter R. Ebeling, M.D., John D. Wark, Ph.D., Peter Mitchell, M.Med., Chris Whithall, M.B., B.S., Stephen Greensli, D. Phil., Margaret P. Staples, Ph.D., and Bridie Murphy, B.Sc.

N Engl J Med
Volume 361(6):5
August 6, 2009
Scores on Measures of Overall Pain, Pain at Night and at Rest, Quality of Life Questionnaire Assessment of Quality of Life, and Disability Questionnaire


Original Article
A Randomized Trial of Vertebroplasty for Osteoporotic Spinal Fractures


N Engl J Med
Volume 361(6):557-568
August 6, 2009

Secondary Outcome Measures at 1 Month (Intention-to-Treat Analyses)
Are vertebroplasty/kyphoplasty safe and effective

- Who should receive them?
- Which is more effective / safe?
- Patient selection
  - Timing after fracture
  - Does severity or number of fractures influence outcome?

What about Generic Alendronate?

- Apotex, Inc.
- Barr Pharmaceuticals, Inc.
- Cobalt Laboratories, Inc.
- Dr. Reddy's Laboratories, Ltd.
- Mylan Pharmaceuticals, Inc.
- Barr Pharmaceuticals, Inc.
- Teva Pharmaceuticals
Requirements for Generic Drugs
To gain FDA approval, a generic drug must:

• Contain the same active ingredients as the innovator drug (inactive ingredients may vary)
• Be identical in strength, dosage, and route of administration
• Have the same use indications
• Be bioequivalent

Generic Alendronate: Concerns

• While drugs must be bioequivalent, the FDA allows a variation of 20% of bioavailability.
• This is a range from 80% - 125% AUC, where there is considered to be no statistically significant difference.

Fosamax vs Generic Alendronate

• 186 post menopausal women
• T score < -2.5
• 12 – 36 months prior Bisphosphonate therapy

Treatment
1. Brand Fosamax 70 mg/wk
2. Generic Alendronate 70 mg/wk
3. Actonel 35 mg/wk

Ringe J. Rheumatol Int. 2009 May 9
L/S Spine BMD Change

Hip BMD Change

12 Month % GI Side Effects
What Should Clinicians do About Generic Alendronate?

- Use only in patients who are likely to be compliant with weekly bisphosphonates
- Consider other alternatives in “high risk patients”
- Closely monitor response with BMD or biochemical markers

Is it safe to use bisphosphonates with abnormal renal function?

Zoledronic Acid:
Renal Safety in HORIZON-PFT

- Short term: 9-11 day post-dose monitoring in > 5000 patients
- Transient rise in serum creatinine in 1.8% of patients (vs 0.9% placebo) with resolution and all patients redosed
- Overall, no cumulative impact on renal function over 3 years

2. Rendell M, Livesey and Johnson (patient information); East Hanover, Nj: Novartis Pharmaceuticals Corp, June 2008.
Zoledronic Acid: Post-Marketing Renal Safety

- There have been 25 cases of ARF reported to the FDA in patients given Zoledronic acid as of July 2009
- Zoledronic Acid is not indicated in patients with a creatinine clearance of < 35 ml/min

What about Oral bisphosphonates and CKD: Risedronate

Miller PD, Roux C, Boonen S, et al. J Bone Miner Res. 2005;20:2105-2115 retrospective analysis of data from nine randomized controlled trials that included a total of 8,996 patients.

Osteonecrosis of the Jaw

- A confirmed case of bisphosphonate-associated ONJ was defined as an area of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health care provider
  - in a patient who was receiving or had been exposed to a bisphosphonate
ONJ Comparative Risks

- Any Fragility Fracture (1)
- Hip Fracture (1)
- Anaphylaxis from PCN
- Death by MVA: 11
- Death by Murder: 0
- ONJ - Osteoporosis Pt.: 0.7
- Death by Lighting in NM: 0.6

(1) Women age 65-69 (from Swedish National Bureau of Statistics and database of Olmsted County, MN, USA.)

M. Lewiecki 2007

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Fosamax: Is Long Term Use Linked to Subtrochanteric Femoral Fractures?

ABC News
Good Morning America
March 9, 2010

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Atypical Fractures of Femoral Shaft

- Transverse fractures of the femoral shaft
- Bilateral in 2/3 of patients
- Delayed healing or non-healing common
- Prolonged use (> 5 years) of alendronate +/- other anti-resorptive medications
- Severely suppressed bone turnover?
One study compared the bone structure of 61 women with osteoporosis taking bisphosphonates for > 4 years to 50 patients taking calcium and vitamin D supplements. There was an association between prolonged therapy and "declining cortical bone structural integrity."

The second study, looked at bone samples taken from 21 post-menopausal women treated for femoral fractures. 12 patients had taken bisphosphonates (average of 8.5 yrs) - 9 hadn't been treated with the drugs. Subjects taking bisphosphonates had a reduction in "bone tissue heterogeneity" compared with women not receiving the drugs.
Subtrochanteric and Diaphyseal Femur Fractures in Patients Treated With Alendronate: A Register-Based National Cohort Study

• Analyzed data from 11,944 patients with osteoporosis
• Atypical subtrochanteric femur fractures had many similar features in common with classical osteoporotic hip fractures, including patient age, gender, and trauma mechanism.
• The data showed that patients taking bisphosphonates and those not taking bisphosphonates had similar numbers of atypical subtrochanteric femur fractures relative to classical osteoporotic hip fractures


Subtrochanteric and Diaphyseal Femur Fractures in Patients Treated With Alendronate:

Subtrochanteric Fractures: Results from the HORIZON-Recurrent Fracture Trial

• 2127 men and women with hip fractures
• Compared baseline characteristics of patients with subtrochanteric femoral fractures and compared them to patients with other types of incident hip fracture

Subtrochanteric Fractures: Results from the HORIZON-Recurrent Fracture Trial

• At baseline, a total of 106/2127 (5.0%) patients had sustained subtrochanteric fractures
  – The mean age, age, sex and BMI were similar between groups.
  – Femoral neck and total hip BMD, and distribution of femoral neck BMD were similar between groups.
  – There were no clinically relevant differences in concomitant diseases or medications (glucocorticoids, anticonvulsants or psychoactive drugs) between groups.


Subtrochanteric Fractures: Results from the HORIZON-Recurrent Fracture Trial

• This post hoc analysis demonstrated that subtrochanteric fractures are not uncommon and do occur in bisphosphonate naive patients, though it failed to show factors that would identify those at greater risk for subtrochanteric fracture


Subtrochanteric Fractures: VA Retrospective Study

• Reviewed 8,000 hip fracture classifications in VA system over past 10 years.
• 9% of all hip fractures were “subtrochanteric”
• No difference in incidence between those exposed or never exposed to bisphosphonates

Saag et al. ASBMR 2009
FDA Drug Safety Communication: Ongoing safety review of oral bisphosphonates and atypical subtrochanteric femur fractures March 10, 2010

"At this point, the data that FDA has reviewed have not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures".

FDA recommends that Patients should:

• Not stop taking medication unless told to do so by your healthcare professional.
• Talk to their healthcare professional if they develop new hip or thigh pain, or have any concerns with your medications.
• Report any side effects with bisphosphonates to FDA’s MedWatch program

FDA recommends that Healthcare Professionals should:

• Be aware of the possible risk of atypical subtrochanteric femur fractures in patients taking oral bisphosphonates.
• Continue to follow the recommendations in the drug label when prescribing oral bisphosphonates.
• Discuss with patients the known benefits and potential risks with using oral bisphosphonates.
• Report any adverse events with the use of bisphosphonates to FDA’s MedWatch program
**Bisphosphonate Holiday?**

**FIT and FLEX**
- Time Between FIT and FLEX: 1 to 2 years
- FIT: 3 to 4.5 years
- FLEX: 5 years

Year

**FLEX: Study Timeline**

F = FIT; FL = FLEX.

**Lumbar Spine BMD From Beginning of FIT to Completion of FLEX**

Mean Percent Change From FIT Baseline, %

F = FIT; FL = FLEX.
Total Hip BMD Change From Beginning of FIT to Completion of FLEX

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

FLEX—Incidence of Fractures

Abbreviations: ALN, alendronate; PLB, placebo.
FLEX: Study Design

When to Consider a Bisphosphonate Holiday

- When patient never needed treatment in the first place
  - Retrospective application of NOF guide

- After good BMD response to at least 5 years treatment and fracture risk no longer high
  - No fracture, T-score > -2.5

- Continue treatment in high-risk patients
  - Previous fractures, T-score ≤ -2.5 and below

When to End a Bisphosphonate Holiday

- Not clear
- Possible approaches
  - Arbitrarily restart treatment after 1–2 years
  - Monitor BMD/BTM every 6–12 months and restart treatment when significant decrease in BMD or increase in BTM
- Reconsider treatment plan if fracture or change in clinical status
New FDA-approvals for Glucocorticoid-induced Osteoporosis

- Alendronate
- Risedronate
- Zoledronic Acid
- Teriparatide

Zoledronic Acid in GIOP Prevention Subpopulation

![Graph showing the change in % change from baseline for Zoledronic Acid in GIOP Prevention Subpopulation.](image)

Graphs present least squares means and 95% confidence intervals. *P < .05, between treatment comparisons.


Zoledronic acid in GIOP Treatment Subpopulation

![Graph showing the change in % change from baseline for Zoledronic Acid in GIOP Treatment Subpopulation.](image)

Graphs present least squares means and 95% confidence intervals. *P < .05, between treatment comparisons.

**Teriparatide Versus Alendronate for Treatment of Glucocorticoid-induced Osteoporosis: 36-month Results**


**Study Design**

<table>
<thead>
<tr>
<th>Screening Phase</th>
<th>18-month Primary Phase</th>
<th>18-month Continuation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teriparatide 20 $\mu$g/day + oral placebo</td>
<td>Teriparatide 20 $\mu$g/day + oral placebo</td>
<td></td>
</tr>
<tr>
<td>Alendronate 10 mg/day + placebo injection</td>
<td>Alendronate 10 mg/day + placebo injection</td>
<td></td>
</tr>
<tr>
<td>Calcium and vitamin D</td>
<td>Calcium and vitamin D</td>
<td></td>
</tr>
</tbody>
</table>

**Lumbar Spine BMD**

<table>
<thead>
<tr>
<th>Months</th>
<th>Teriparatide</th>
<th>Alendronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>159 154 173</td>
<td>159 148 131</td>
</tr>
<tr>
<td>3</td>
<td>162 158 170</td>
<td>156 146 136</td>
</tr>
<tr>
<td>6</td>
<td>165 160 172</td>
<td>159 148 136</td>
</tr>
<tr>
<td>9</td>
<td>168 163 178</td>
<td>162 156 136</td>
</tr>
<tr>
<td>12</td>
<td>171 167 184</td>
<td>165 157 136</td>
</tr>
<tr>
<td>15</td>
<td>174 172 190</td>
<td>168 158 136</td>
</tr>
<tr>
<td>18</td>
<td>177 175 196</td>
<td>171 160 136</td>
</tr>
</tbody>
</table>

* $P<0.05$; ‡ $P<0.001$ Teriparatide vs. Alendronate

BMD = bone mineral density, g/cm$^2$
**Proximal Femur BMD**

![Graph showing Proximal Femur BMD comparison between Teriparatide and Alendronate.](image)

*P<0.05, †P<0.01, ‡P<0.001 Teriparatide vs. Alendronate* 

**Number of Patients With New Vertebral Fractures**

<table>
<thead>
<tr>
<th></th>
<th>Alendronate</th>
<th>Teriparatide</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral radiographic</td>
<td>13 (7.7%)</td>
<td>3 (1.7%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Clinical vertebral**</td>
<td>4 (2.4%)</td>
<td>0</td>
<td>0.037</td>
</tr>
<tr>
<td>Mild</td>
<td>7 (4.1%)</td>
<td>1 (0.6%)</td>
<td>0.026</td>
</tr>
<tr>
<td>Moderate</td>
<td>2 (1.2%)</td>
<td>2 (1.2%)</td>
<td>0.963</td>
</tr>
<tr>
<td>Severe</td>
<td>4 (2.4%)</td>
<td>0</td>
<td>0.039</td>
</tr>
</tbody>
</table>

Saag et al. Arthritis and Rheumatism 2009

**2010 American College of Rheumatology Guidelines for Glucocorticoid-induced Osteoporosis**

- Will include Zoledronic Acid as well as Teriparatide as treatment options
- Will incorporate Clinical Risks for Fracture as well as T-scores (similar to FRAX) to stratify low versus high risk patients
**Denosumab for Postmenopausal Osteoporosis: FREEDOM Study**

- **BMD**
  - Lumbar spine ↑ 9.2% (P < .0001)
  - Total hip ↑ 6.0% (P < .001)
- **BTM**s
  - CTX ↓ 72% (P < .001)
- **Fracture risk**
  - Vertebral ↓ 68% (P < .0001)
  - Hip ↓ 40% (P = .036)
  - Nonvertebral ↓ 20% (P = .011)


**FREEDOM trial: Adverse Events**

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Denosumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>92.8%</td>
<td>93.1%</td>
</tr>
<tr>
<td>Infections</td>
<td>52.3%</td>
<td>54.4%</td>
</tr>
<tr>
<td>Cancer</td>
<td>4.8%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>0%</td>
<td>0.1%</td>
</tr>
<tr>
<td>ONJ</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

FREEDOM Trial: Serious Adverse Events

<table>
<thead>
<tr>
<th>SAEs</th>
<th>Denosumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>25.8%</td>
<td>25.1%</td>
</tr>
<tr>
<td>Infections</td>
<td>4.1%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Cancer</td>
<td>3.7%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.7%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Deaths</td>
<td>1.8%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>4.8%</td>
<td>4.6%</td>
</tr>
</tbody>
</table>

Abbreviation: SAEs, serious adverse events.

Emerging Therapies

- Antiresorptive (anti-catabolic)
  - Denosumab
  - Lasofoxifene
  - Bazedoxifene
  - CE/bazedoxifene
  - Odanacatib
  - New delivery systems

- Osteo-anabolic (bone-forming)
  - Sclerostin inhibitor
  - Variations of parathyroid hormone
  - Calcium-sensing receptor antagonist (calcilytic)
  - New delivery systems
  - Combinations of antiresorptive and anabolic

Resorbing Osteoclast

Abbreviation: N, nucleus; G, Golgi; R, rough endoplasmic reticulum; NCC, non-calcium-containing crystal; C, calcium-containing crystal; AM, actin microfilaments; MN, microtubules; V, vesicles.
Signals Determining Differentiation Toward Osteoblasts and Acting on Mature Osteoblasts to Enhance Bone Formation

Under the influence of Wnt and BMP, undifferentiated mesenchymal cells differentiate toward cells of the osteoblast lineage.

Abbreviations: BMP, bone morphogenetic protein; PTH, parathyroid hormone.

Wnt Antagonists

The extracellular Wnt antagonists prevent Wnt signaling. Dkkopf-1 (Dkk-1) in association with Kremen and sclerostin bind LRPS and LRP6.