Osteoporosis Update
ACP Oregon Chapter
November 9th, 2018
Sarah Hopkins
Providence Medical Group Endocrinology East

No disclosures.
Goals

• Review screening recommendations and workup of secondary causes of osteoporosis
• Focus on Common Questions Regarding Treatment:
  – What about calcium and Vitamin D?
  – Are the medications effective?
  – What are the risks of the medications and how do these risks compare to the benefits?
  – How do we know if the medication is working?
  – How long will I need to be on this medication?
  – What comes next if the treatment does not work?

65 y/o woman with no significant history here for annual exam. She is very active, eats a healthy diet. No history of fractures.

“Do I really need a bone density right now?”
Bone Remodeling Cycle


Changes in bone mass with age

Adapted from J Compston 1990
Osteoporosis

Normal bone

Osteoporotic bone

Osteoporosis Fracture Impact

Women with fracture

Men with fracture
Osteoporosis and Age

Figure 3. Osteoporosis or low bone mass at the femur neck or lumbar spine, by age in adults aged 50 years and over

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Men %</th>
<th>Women %</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>32</td>
<td>54</td>
</tr>
<tr>
<td>60-69</td>
<td>32</td>
<td>65</td>
</tr>
<tr>
<td>70-79</td>
<td>45</td>
<td>66</td>
</tr>
<tr>
<td>80+</td>
<td>66</td>
<td>68</td>
</tr>
</tbody>
</table>

* p < 0.05 compared with preceding age group within sex and skeletal site category.
* p = 0.05 for trend by age group within sex for both osteoporosis and low bone mass.


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NOF and AACE Screening Guidelines

50+
- you break a bone after age 50;

65+
- you are a woman age 65 or older;
- you are a postmenopausal woman under age 65 with risk factors;

65-
- you are a man age 65-70 with risk factors;

50-69
- you are a woman of menopausal age with risk factors;

70+
- you are a man age 70 or older.


http://www.fvortho.com/wp-content/themes/fvo/img/osteo/info-orthopedics.gif
She agrees to bone density:

- Screening bone density shows T score of -2.8 at femoral neck and -2.4 at spine.
- No history of fractures.

What does this mean?

Low T scores ≠ Age Related Osteoporosis

- Osteomalacia
  - Vitamin D deficiency, low calcium intake
  - Hypophosphatasia
  - Metabolic bone disease in CKD
  - Post-bariatric surgery, GI malabsorption

- Endocrine Disorders:
  - Hyperparathyroidism, Hyperthyroidism, Cushing’s Syndrome, hypogonadism
  - Anorexia Nervosa
  - Multiple myeloma

Medications

- Glucocorticoids
- Aromatase inhibitors
- Depo-Provera
- Methotrexate
- Anticonvulsants
- Chemotherapy
- GnRH agonists
- Cyclosporine
- Tacrolimus
- Fall risk:
  - BP meds
  - Sedatives

Back to our patient...

- PMHx:
  - GERD
  - No history of fractures
  - No history of kidney stones
- Fam Hx:
  - No hip fracture
  - No osteoporosis
- Meds:
  - None
  - No calcium/Vitamin D supplements but has two servings of dairy daily

- Physical Exam:
  - Height stable
  - No kyphotic/scoliotic changes or spinal tenderness
  - Stands with ease, good balance and gait
Labs:

- Normal CBC, CMP (specifically, creatinine, alk phos, calcium), phosphorus, Vitamin D, TSH

Would consider if risk factors (UPEP, SPEP, PTH, 24 hour urine calcium)

Universal Recommendations

- Calcium intake 1200mg women $\geq$ 51, men $\geq$ 71 and 1000mg for men 50-70
- Vitamin D 800-1000IU
- Weight bearing exercises
- Fall risk assessment
- Smoking cessation and avoidance of excess alcohol

"I have heard calcium does not prevent fractures and causes heart disease and kidney stones."

Table 1: Summary of selected randomized controlled trials that compared CVD outcomes in calcium supplemented and placebo groups. Studies were categorized as follows: 1) observational studies, 2) randomized controlled trials. CVD = cardiovascular disease.

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<th>Study reference</th>
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Osteoporosis Consensus Guidelines

- We know calcium and Vitamin D deficiencies are associated with poor bone health
- Calcium and Vitamin D may lead to modest reductions in fracture risk
- Benefit is greatest in those at highest risk of insufficiencies
- There is insufficient evidence to prove calcium supplementation targeting normal daily recommended amounts increases cardiovascular risk


TOP PICKS
Best Calcium Supplements for a Younger You


http://www.thrombocyte.com/best-calcium-supplements/
Brief Calcium/Vit D Advice:

- **Calcium:**
  - Don’t over do it - Through supplements and dietary calcium, target 1200mg (women > 50)
  - Average dairy serving has 300mg calcium
  - Keep it simple
  - Calcium carbonate most potent/cost effective (40% elemental calcium versus 20% with calcium citrate)

- **Vitamin D:**
  - Greatest benefit seen in maintaining level 20-30ng/dl

“Can I just focus on calcium, Vitamin D and exercise? Do I really need a medication? I feel great.”
Bone Specific Therapy Candidates

- History of hip or vertebral fracture
- T score < -2.5 at hip or spine
- Post-menopausal women with T score -1.0 to -2.5 with FRAX score of ≥ 20% for major osteoporotic fracture or ≥ 3% hip fracture at 10 years.


“Aren’t the medications dangerous? I’ve heard they cause fractures.”
Therapy Highlights

- Benefits >>>> Risks

- Effective fracture reduction:
  - Vertebral 50-70%
  - Hip 40-50%
  - Non-Vertebral 20-35%

- Fracture reduction effective early in treatment

- Low risks
  - Atypical femur fracture, osteonecrosis of the jaw

- Duration of therapy/Treatment response

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Antiresorptive Comparison

<table>
<thead>
<tr>
<th>Medication</th>
<th>Absolute Risk Reduction</th>
<th>Relative Risk Reduction</th>
<th>NNT to prevent 1 Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vert Fx</td>
<td>Hip Fx</td>
<td>Vert Fx</td>
</tr>
<tr>
<td>Alendronate (FIT I)</td>
<td>7.1%</td>
<td>1.1%</td>
<td>47.1%</td>
</tr>
<tr>
<td>Risedronate (VERT NA)</td>
<td>5.0%</td>
<td>0.4%</td>
<td>30.7%</td>
</tr>
<tr>
<td>Zoledronic Acid (HORIZON PFT)</td>
<td>7.6%</td>
<td>1.1%</td>
<td>70%</td>
</tr>
<tr>
<td>Ibandronate (BONE)</td>
<td>4.9%</td>
<td>NA</td>
<td>62%</td>
</tr>
<tr>
<td>Denosumab (FREEDOM)</td>
<td>4.9%</td>
<td>0.5%</td>
<td>68%</td>
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Harris ST et al. JAMA. 1999;282:1341-1352

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11/4/2018
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    - Hip 40-50%
    - Non-Vertebral 20-35%
  - Fracture reduction effective early in treatment
  - Low risks
    - Atypical femur fracture, osteonecrosis of the jaw
  - Duration of therapy/Treatment response

Alendronate: FIT TRIAL

Clinical Vertebral Fracture

- NNT to prevent fracture in 3 years: 14

Hip Fracture

- NNT to prevent fracture in 3 years: 90

Zoledronic Acid: HORIZON Study


Denosumab: FREEDOM Study

### Antiresorptive Comparison

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<tr>
<th>Medication</th>
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"But isn’t alendronate dangerous? I have heard it causes fractures.”
Bisphosphonate Safety

<table>
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<tr>
<th>Proven association between risk and prolonged use</th>
<th>No association with prolonged use</th>
<th>Associations without clear causality or relationship to duration of use</th>
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<tbody>
<tr>
<td>Atypical femur fracture</td>
<td>GI upset (PO)</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td>Flu like symptoms (IV)</td>
<td>Osteonecrosis of the jaw</td>
</tr>
<tr>
<td></td>
<td>Hypocalcemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bone pain</td>
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Atypical Femur Fracture

- Low trauma subtrochanteric or femoral shaft fracture
- Non-comminuted
- Transverse or short oblique in orientation
- Often prodromal symptoms of dull pain in groin or thigh
Atypical Femur Fracture

- Associated with bisphosphonates and denosumab
- Risk increased with prolonged use
- Risk factors:
  - Female sex
  - Asian ethnicity
  - Hypophosphatasia
  - Vitamin D deficiency/osteomalacia
  - Glucocorticoid use
  - Proton-pump inhibitor use


Atypical Femur Fracture

- Kaiser Cohort Study looked at 11,466 patients with femoral fracture
  - 142 atypical, with 10% not on bisphosphonate
- 2 year risk: 1.78/100,000
- 5 years: 20/100,000
- 8-9.9 years: 113/100,000

Atypical Femur Fracture: NNT vs NNH

Table 3. Number of Patients Who Would Need to Be Treated for 3 Years with Bisphosphonates to Prevent One Fracture versus the Hypothetical Number Associated with an Increase of One Atypical Femur Fracture.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. Needed to Treat (3 yr)</th>
<th>No. of Events Prevented per 1000 Patients Treated (3 yr)</th>
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<tbody>
<tr>
<td>Type of fracture</td>
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<tr>
<td>Any nonvertebral, including hip</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>Hip</td>
<td>90</td>
<td>11</td>
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<tr>
<td>Vertebral fracture (morphometric)</td>
<td>14</td>
<td>71</td>
</tr>
<tr>
<td>Any fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothetical relative risk of atypical femur fracture</td>
<td>No. Needed to Harm (3 yr)</td>
<td>No. of Atypical Femur Fractures Associated with Treating 1000 Women for 3 Yr</td>
</tr>
<tr>
<td>1.2</td>
<td>43,300</td>
<td>0.02</td>
</tr>
<tr>
<td>1.7</td>
<td>12,400</td>
<td>0.03</td>
</tr>
<tr>
<td>2.4</td>
<td>6,200</td>
<td>0.16</td>
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<tr>
<td>11.8</td>
<td>800</td>
<td>1.25</td>
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Osteonecrosis of the Jaw

- Incidence 1/10,000-250,000 patient-treatment years.
- In Phase 3 clinical trials the extremely low incidence rate did not appear to be in excess of placebo.
- Risk factors: Poor oral hygiene, glucocorticoids, or chemotherapy exposure.

Ott, SM. Clinic J of Med. 2011
American Dental Association position statement: “the decision to discontinue therapy should be a medical decision based primarily upon the risk for skeletally related events (eg, fractures) secondary to low bone density, not the potential risk of osteonecrosis of the jaw.”

Ott, SM. Clinic J of Med. 2011

• You elect to try alendronate given low price and efficacy at hip and spine.
“How do we know if it’s working?”

Monitoring

• Annual follow up:
  – Review risk factors, annual creatinine
  – Ensure adequate calcium, Vitamin D, weight bearing exercises
  – Accurate height measurement
    • 2cm+ height loss → vertebral imaging
  – DEXA?
ACP Guidelines

• “ACP recommends against bone density monitoring during the 5-year pharmacologic treatment period for osteoporosis in women,” is noted as not having a strong evidence base (“Grade: weak recommendation; low-quality evidence”)


AACE Response

• Bone density 1-2 years after starting therapy
• Why?:
  – Identify individuals who are not responding to therapy
  – These individuals often have undiagnosed disorders contributing to bone loss, or may have absorption or adherence issues.
  – Continued treatment may not be appropriate

Back to our patient …

- 2 years later her height has declined 2.3 cm since starting therapy
- Bone density demonstrates improvement in T score at L spine to -2.3, femoral neck -2.7
- Spine X-ray reveals new compression fracture at T12

“Should I stop the alendronate and start something else?”
NOF Treatment Failure

- 2+ new fragility fractures
- 1 new fracture +
  - a significant decrease in BMD and/or
  - elevated serum βCTX or PINP at baseline with no significant reduction during treatment
- Significant decrease in BMD and no significant decrease in serum βCTX or PIN


3 years later:

- No further fractures
- Height stable
- T score lumbar spine -2.3, hip -2.7
“Isn’t it safest to stop the drugs after 5 years of treatment?”

Duration of Therapy

• ACP guidelines recommend stopping therapy after 5 years.
• AACE and NOF recommend duration of therapy be individualized
Key Considerations with Long Term Therapy

- Continued benefits with long term therapy
- Benefits decline after stopping treatment
- For individuals most at risk for fractures benefits > Risks

Alendronate: FLEX Trial

Vertebral Fractures: NNT 32.3

No change in non-vertebral fractures

FLEX Non-Vertebral Fracture Reduction when T score < -2.5

-50% reduction in non-vertebral fractures when T score < -2.5
-No benefit if T score < -2.0

Schwartz A et al., *J Bone Miner Res.* 2010; 25:976–82

Reclast: Horizon Extension

Long-term Denosumab Therapy
Vertebral and Non-vertebral Fractures

Persistent reduction in fracture risk

Key Considerations with Long Term Therapy

- Continued benefits with long term therapy
- Benefits decline after stopping treatment
- For individuals most at risk for fractures benefits > Risks

Bone HG et al. Lancet Diabetes Endocrinol 2017;5:513-23
Bisphosphonates

FLEX

HORIZON Extension


Stopping Denosumab

Quick loss of bone density gains with drug discontinuation

When stopped, the effects of denosumab on bone remodeling is quickly reversed. This can be attenuated by starting another therapy. The importance of getting denosumab injections as scheduled should be emphasized. If treatment is to be discontinued, alternate therapy should be considered.

Takeaway

- Fracture reduction occurs within months
- Fracture reduction persists with long term therapy (up to 10 years)
- Fracture risk increases when therapy is stopped
  - Denosumab (and anabolics) immediately
    • Should use bisphosphonate after
  - Bisphosphonates within years
National Osteoporosis Statement

- Duration decisions should be individualized.
- After 3-5 years of treatment, risk assessment should be performed.
- Modest risk for fracture: Consider treatment holiday.
- High risk of fracture → Continue therapy with bisphosphonate or alternative.


AACE

**Mild osteoporosis** → Consider a “drug holiday” after 4-5 years of therapy

**High fracture risk** → Consider a “drug holiday” of 1-2 years after 10 years of treatment

(Grade B; BEL 1)

Back to our patient..

- Year 7 of alendronate falls and suffers left hip fracture
- Bone density unchanged
- She reports taking pills weekly

2 Fractures = Treatment Failure

Treatment Options

- IV bisphosphonate
- Denosumab
- Anabolic Therapy
Oral bisphosphonate → Denosumab versus Zoledronic Acid

Denosumab with greater mean % change in areal BMD from baseline to 12 months.


Alendronate to Denosumab

- Greater BMD increases at hip and spine in denosumab versus alendronate (1.9% vs. 1.05% at hip p < 0.001)
- Denosumab had greater decrease in markers of bone turnover

“Should we consider a bone building drug now?”

**Teriparatide vs Risedronate (VERO Study)**

In women with postmenopausal osteoporosis at high risk of fracture, teriparatide reduced vertebral, clinical and non-vertebral fractures more than did risedronate at 12 and 24 months.

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**A** Incidence of new vertebral fractures

- Teriparatide
- Risedronate

Relative risk: 0.44

(95% CI 0.30-0.68)

*p* = 0.0001

57% percent of participants were on bisphosphonate therapy previously.

**B** First clinical fracture

57% percent of participants were on bisphosphonate therapy previously.

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Teriparatide $\rightarrow$ Alendronate

Teriparatide $\rightarrow$ placebo: Decline
Teriparatide $\rightarrow$ alendronate: Continued gains
Combination therapy $\rightarrow$ Minimal effect

**Osteoporosis: Long-term Treatment Plan**

- **Raloxifene**
  - When concerned about hip fracture
  - After 18-24 months
  - Low risk → Consider drug holiday
  - High risk → Continue therapy

- **Bisphosphonate**
  - After 18-24 months
  - Low risk → Re-treat
  - High risk → Continue therapy

- **Teriparatide, abaloparatide**
  - After 18-24 months
  - Low risk → Denosumab
  - High risk → Bisphosphonate for 2 years

- **Denosumab**
  - If “target” is met
  - Low risk

**Review**

- **Therapies:**
  - Quickly effective to reduce fractures
    - Vertebral 60-70% (NNT 10-20)
    - Hip 40-50% (NNT 80-90)
    - Non-Vertebral 20-35% (NNT 30-40)
  - Continued benefits with long term therapy
  - Benefits decline after stopping treatment
    - Rapid decline with denosumab and PTH/PTHrP therapy for which follow up treatment with other anti-resorptive advised
    - Low risk
Review

• Treatment failure:
  – 2+ new fragility fractures
  – 1 new fracture + significant decrease in BMD and/or elevated serum βCTX or PINP at baseline with no significant reduction during treatment

• Second line therapy options: IV bisphosphonate, denosumab, or PTH/PTHrP therapy
  – Sequence matters (no PTH after denosumab)

Thank you
Questions

Which of the following is an example of treatment failure in osteoporosis and would warrant consideration of alternate anti-osteoporosis therapy?

A. Vertebral fractures of L1 and L2 within 6 months of initiating anti-osteoporosis medication
B. 3 new metatarsal fractures and single hip fracture while on anti-osteoporosis medications for 3-5 years.
C. Hip fracture 8 months and T12 fracture 2 years after starting anti-osteoporosis therapy
D. 3% decline in BMD at spine over 3 years of anti-osteoporosis medication

Questions

Which of the following osteoporosis medications can be stopped without risk of rapid bone loss?

A. Teriparatide
B. Alendronate
C. Denosumab
D. Abaloparatide
Extra Slides

Teriparatide $\leftrightarrow$ Denosumab

- Teriparatide $\rightarrow$ Denosumab, additional gains
- Combination therapy: Additional gains
- Denosumab $\rightarrow$ Teriparatide: Quick decline

Leder BX. JBMRPLUS. 2018:2;62-68.
Ca/Vit D + Bone Density: WHI

No difference at spine or total body

Jackson et al. NEJM 2006;669-683.

WHI Fracture Results

Table 2. Effect of Calcium with Vitamin D Supplementation on Clinical Outcomes, According to Randomly Assigned Group.*

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Calcium + Vitamin D</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)†</th>
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<tbody>
<tr>
<td>Intention-to-treat analysis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Follow-up time — yr</td>
<td>7.0±1.4</td>
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<td>Rate of fracture — no. of cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(annualized %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>175 (0.14)</td>
<td>199 (0.16)</td>
<td>0.88 (0.72–1.08)</td>
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<td>Clinical vertebral</td>
<td>181 (0.14)</td>
<td>197 (0.15)</td>
<td>0.90 (0.74–1.10)</td>
</tr>
<tr>
<td>Lower arm or wrist</td>
<td>565 (0.44)</td>
<td>557 (0.44)</td>
<td>1.01 (0.90–1.14)</td>
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<td>Total</td>
<td>2102 (1.64)</td>
<td>2158 (1.70)</td>
<td>0.96 (0.91–1.02)</td>
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Analysis excluding follow-up

Time for participants 6 mo after nonadherence detected

Follow-up time — yr 3.8±2.9 3.9±2.9

Rate of fracture — no. of cases (annualized %)

| Hip                              | 68 (0.10)          | 99 (0.14) | 0.71 (0.52–0.97)       |
| Clinical vertebral               | 91 (0.13)          | 104 (0.15) | 0.89 (0.67–1.19)       |
| Lower arm or wrist               | 312 (0.45)         | 308 (0.43) | 1.05 (0.90–1.23)       |
| Total                            | 1139 (1.63)        | 1222 (1.72) | 0.94 (0.87–1.02)       |
11 year follow up WHI

- No difference in rate of hip fracture over total ITT analysis post-randomization
  - Adherent women had 23% reduction in hip fracture
- Decrease in vertebral fractures HR 0.87 (CI 0.76-0.98 p 0.6): 4 fewer fractures / 10,000 taking supplements
- No difference in rates of breast cancer, heart disease, death


National Osteoporosis Foundation, AACE, and American Society for Bone and Mineral Research all recommend calcium and Vitamin D use
“What about the bone building drugs?”

Teriparatide: Fracture Prevention Trial

NNT Vertebral Fracture: 10
NNT Non-Vert Fracture: 33

Abaloparatide: ACTIVE Trial


Anabolic Therapies

- SQ injections in prefilled pen
- First injection should be observed in lying or seated position for possible orthostatic hypotension
- Monitor for hypercalcemia. If > 11, do alternate day dosing and stop if this does not lower calcium < 11

- Use limited to 2 years due to theoretical concerns of increased rates of osteosarcoma seen in rats.
- Gains quickly decline after stopping treatment

### Comparison of Medications for Osteoporosis

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When to Consider Anabolic Therapies as First Line

- Patients with severe osteoporosis who are likely to need many years of therapy/different therapies
  - Why? – Sequence matters
- Steroid induced osteoporosis
  - Steroids predominantly inhibit osteoblast pathway
**Teriparatide ➔ Alendronate**

- Teriparatide ➔ placebo: Decline
- Teriparatide ➔ alendronate: Continued gains
- Combination therapy ➔ Minimal effect


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Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate

Michael McClung a, b, Robert Recker b, Paul Miller c, Darrell Fiske d, Jerome Minkoff e, Audrey Kriegman f, Wenchun Zhou f, Mathews Adera f, Jenny Davis f

- Bone resorption markers were decreased in zoledronic group at 3 months, similar at 6 months, and slightly increased ➔ 12 months
- No significant difference in lumbar spine BMD between groups at 12 months
- 78.7% patients preferred IV treatment

McClung et al. 2007;41:122-128.