Advances in osteoporosis

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Potential conflicts of interest

None

GOALS

- When to screen/treat?
  - BMD
  - FRAX
- Rx
  - Ca/D- concerns about CVD
  - Drugs- old
    - Bisphosphonate concerns
  - Drugs - new
    - Odanacatib – almost here
    - Romosozumab – bone builder, but still a way off!
New NOF GUIDELINES

- Screen
  - women after 65, and men after 70
  - >50 if additional risk factors are present
- Treat men or women after age 50 if
  - Vertebral or hip fx, OR
  - Any T-score < -2.5, OR
  - T-score -1 to -2.5 and
  - 10 year hip fracture risk is >3%

http://www.shef.ac.uk/FRAX/
Clarification of risk factors

5. Previous fracture - a previous fracture in adult life occurring spontaneously, or a fracture arising from trauma which, in a healthy individual, would not have resulted in a fracture

8. Glucocorticoids – history of use of prednisone at a dose of 5 mg/day for >3 months

10. Secondary osteoporosis
   – ignore in a pt who had a BMD.

NOF GUIDELINES

Screen
– women after 65, and men after 70
– >50 if additional risk factors are present

Treat men or women after age 50 if
– Vertebral or hip fx, OR
– Any T-score <-2.5 (osteoporosis), OR
– T-score –1 to –2.5 (osteopenia) and
– 10 year hip fracture risk is >3%,
   http://www.shef.ac.uk/FRAX/

USPSTF GUIDELINES

Screen
– women after 65, and men after 70
– Women menopause-65 and men 50-70 if pre-BMD FRAX predicts MOF (major osteoporotic fracture) risk >9.3%
   http://www.shef.ac.uk/FRAX/
Of pts with low (<10%) or moderate (10-20%) MOF risk when calculated without BMD, % who qualify for Rx by NOF criteria after they have a BMD

<table>
<thead>
<tr>
<th>MOF risk- (No BMD)</th>
<th>% who qualify for Rx by NOF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T&lt;-2.5</td>
</tr>
<tr>
<td>Low</td>
<td>17.3%</td>
</tr>
<tr>
<td>Moderate</td>
<td>40.0%</td>
</tr>
</tbody>
</table>

So doing BMD on only patients with MOF>10% would capture ~80% of patients needing Rx, while screening 43% of the population.

Leslie et al, Osteoporosis International 2012;23:75

USPSTF guidelines to use a pre-BMD FRAX

**TOO COMPLICATED!**

No additional benefit for all this trouble.

Interpretation of BMD

**Osteoporosis** – Imminent risk of fracture in the next couple of years, especially if there are pre-existing VCF. All drug trials show a reduction in fracture risk if patients with osteoporosis are treated.

**Osteopenia** – The concern is that with time these patient's will likely get osteoporosis.

No imminent decrease in risk of fracture with treatment, but WE BELIEVE that fracture risk will decrease over time with Rx at menopause.

We treat osteopenic women at or after menopause if life expectancy >10 years.
In patients with BMD without indication for Rx, when do we do the next BMD?

- Hard to say!

- In general patients lose BMD over time, but at a variable rate.
In patients with BMD without indication for Rx, when do we do the next BMD?

- Hard to say!
- In general patients lose BMD over time, but at a variable rate.
- The question is, what is the interval that it takes for TEN PERCENT of patients to make it from osteopenia to osteoporosis, and that should be the scanning interval.
- However, it makes sense that the interval it takes to get to osteoporosis DEPENDS ON HOW CLOSE THE PATIENT IS!

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<table>
<thead>
<tr>
<th>Initial T-score</th>
<th>Interval in years</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2 to -2.49</td>
<td>1</td>
</tr>
<tr>
<td>-1.5 to -1.99</td>
<td>5</td>
</tr>
<tr>
<td>-1 to -1.49</td>
<td>17</td>
</tr>
</tbody>
</table>

Gourlay et al. NEJM 2012;366:225
WHAT interval is 1, 5, or 17 years?

- This is the scanning interval in patients who do NOT qualify for treatment.
- This is not the scanning interval in patients who ARE ON treatment!

Following pts on Rx for osteoporosis-
Aggressive approach

- A small percentage of patients on antiresorptive therapy may be losing BMD, so follow patients with serial BMDs.
- Some pts losing BMD on Rx have a secondary cause, like celiac disease.
- Following patients with serial markers and/or densitometry may provide reinforcement that would improve long-term compliance.

Following pts on Rx for osteoporosis-
Conservative approach

- Patients with osteoporosis treated with anti-resorptive Rx have a decrease in turnover, increase in BMD, and reduction in fracture risk.
- Verify that patient is taking the medication, compliant with usual precautions, is taking adequate vitamin D and calcium, and has no other conditions that cause bone loss.
- Even if we identify pts with suboptimal BMD response to Aln, we do not need to change therapy, because they still have fewer fx than with placebo.
RR of VCF in pts in FIT accdg to changes in hip BMD on Rx, compared with placebo pts in the corresponding percentile (OI 2005;16:842)

VFA (vertebral fracture analysis)
- The densitometer can do an AP and lateral thoraco-lumbar view which is excellent for checking for vertebral fractures
- Excellent resolution up to T7
- This is a separate test with its own CPT code, but costs very little (~$20)

On the left we see a normal lateral VFA showing no VCF as high as we can see (T6).
On the right, we see a lateral VFA with a wedge deformity of T12.
Why was VFA developed?

- Vertebral fractures are common even among patients who otherwise have no indication for treatment based on BMD and FRAX
  - 18% of such patients had unsuspected vertebral fractures
    - Greenspan et al., JCD 2001;4:373

- So the value of VFA is that it identifies patients with skeletal fragility who would benefit from treatment even if the BMD is OK and FRAX are not bad.

Who should have VFA?

- Reasonable pretest probability of finding the VFA (>10%?)
- The finding of vertebral fracture will influence clinical management
1147 men from Geelong had VFA, considered VCF only if ≥ grade 2. Prevalence of VCF in men climbs >10% over age 80.

Pasco et al., OI 2009;20:787.

VFA guidelines – ISCD (International Society for Clinical Densitometry)

Patients should have a VFA if they fulfill ≥1 of the following 4 criteria:

- Age (≥70 for women or ≥80 for men), OR
- Historic height loss ≥4 cm (1.5 inches), OR
- Steroid use (5 mg/d prednisone for 3 months), OR
- Self-reported but unconfirmed vertebral fracture

Calcium and 800 units of vitamin D for the treatment of osteoporosis

NEJM 1992;327:1637
NEJM 1997;337:670
Fracture risk according to 25 OHD levels.
Trough at 50 nmol/L, or 20 ng/dl.

Melhus et al, JCEM 2010; 95:2637

OR for pancreatic cancer in patients according to 25 OHD levels

<table>
<thead>
<tr>
<th>&lt;10</th>
<th>10-15</th>
<th>15-20</th>
<th>20-30</th>
<th>30-40</th>
<th>&gt;40</th>
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<tbody>
<tr>
<td>0.95</td>
<td>0.98</td>
<td>1.04</td>
<td>1.00</td>
<td>1.02</td>
<td>2.12</td>
</tr>
</tbody>
</table>

Pooled 8 case-control studies, multivariate-adjusted. 95% CI of OR for 25 OHD>40 is 1.23-3.64

American Journal of Epidemiology 2010;172:81

Bolland et al, BMJ 2010;341:3691 Metaanalysis of calcium-only trials showed an increase in MI
1460 women randomized to 1200 mg of calcium vs placebo, followed over 10 yrs. Lewis et al, JBMR 2011;26:35

13331 patients from NHANES, cross-sectional study of mortality vs D. Arch Int Med 2008;168:1629

Endocrine Society guidelines

- Intake: 1500-2000 units/day
  - 2-3 times that much for patients at high risk for vitamin D deficiency, such as patients with
    - malabsorption,
    - anticonvulsant use,
    - obesity.
- Desirable levels: 30-60 ng/ml
Women >6 yrs after menopause randomized to 500 mg of calcium vs pbo.

In women with baseline calcium intake <400 mg/d, calcium supplements reduced bone loss.

In women with calcium intake >400 mg/d, no effect of calcium supplements

**Calcium conclusions**

- **Estimate dietary calcium intake**
  - 1 serving (300 mg) =
    - 1 cup of milk, yogurt, beans, collard greens, or almonds
    - 2 cups of ice cream, cottage cheese, or broccoli
    - 1 oz of hard cheese
    - 1 can of sardines or salmon (with bones)
  - if >1000 mg/d, OK (NEJM 1990;323:878)

- Add in supplemental calcium citrate TO GET INTAKE OVER 1000 mg/d

- 1000 units of D daily

**How to put this together?**

- For patients without particular risk of vitamin D deficiency
  - 1000 units of vitamin D daily
  - No need to check levels

- For patients with high risk of vitamin D deficiency
  - 2000 units of vitamin D daily
  - Verify that 25 OHD levels are 30-60 ng/ml, and adjust dose accordingly

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Scorecard

<table>
<thead>
<tr>
<th>Drug</th>
<th>Abbreviation</th>
<th>Brand Name</th>
<th>Class</th>
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<tbody>
<tr>
<td>Alendronate</td>
<td>aln</td>
<td>Fosamax</td>
<td>PO bis</td>
</tr>
<tr>
<td>Risedronate</td>
<td>ris</td>
<td>Actonel</td>
<td>PO bis</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>ibn</td>
<td>Boniva</td>
<td>PO/IV bis</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>zol</td>
<td>Reclast</td>
<td>IV bis</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>ralox</td>
<td>Evista</td>
<td>SERM</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>calc</td>
<td>Miacalcin</td>
<td>Nasal hormone</td>
</tr>
<tr>
<td>Denosumab</td>
<td>den</td>
<td>Prolia</td>
<td>Ab to RANKL</td>
</tr>
<tr>
<td>PTH</td>
<td>PTH</td>
<td>Forteo</td>
<td>Anabolic</td>
</tr>
<tr>
<td>*Odanacatib (ODN)</td>
<td>ODN</td>
<td>ODN</td>
<td>Cathepsin K inh*</td>
</tr>
</tbody>
</table>

Guidelines for treatment of osteoporosis

- First line – Aln-vs others, longer track record, hip fx efficacy, better BMD data, and cheap generic
- Second line – IV zoledronate (better hip fx and BMD data than ralox or ibn) or SQ denosumab
- Third line – ralox or ibn
- Calcitonin nasal spray has minimal effects on BMD, but may benefit pain slightly
- PTH is usually reserved for patients with severe spine osteoporosis, because of best spine BMD data, but cumbersome administration.

Bone et al., NEJM 2004;350:1189
Exposed Necrotic Bone in a Patient Receiving Zoledronic Acid for 6 Months: Maxillary Extractions 4 Months Earlier


ONJ incidence in pts with cancer on monthly IV bisphosphonates. NEJM 2005;353:99

Lo et al., J Oral and Maxillofacial Surgery 2010;68:243

- 13946 Kaiser pts on oral BIS were mailed a survey about dental symptoms; 8572 responded
- All with symptoms were brought in for exam, or dental records reviewed.
- 0.1% (9/8572) met criteria for ONJ
- Critique: "Overestimate!"
  - Pts without ONJ might not have responded
  - There is no comparison to the prevalence of nonhealing exposed bone in pts NOT on BIS

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Park-Wyllie et al, JAMA 2011;305:783

- Risk of subtrochanteric fx increased in pts on BIS
  RR=2.74 (1.25-6.02), but only after >5 yrs duration.
- Absolute risk of subtrochanteric fractures after >5 years of BIS Rx was 0.13%

Almost all of the cases of ONJ or spontaneous femur fractures are in pts on alendronate for >5 years!
Cumulative Incidence of Clinical Vertebral Fractures With Alendronate Supports the Safety of Long-Term Treatment

Suggestions?
- Try to get any jaw SURGERY done prior to bisphosphonate Rx, particularly in pts getting high dose IV.
- Good oral hygiene and dental prophylactic care. (AIM 2006;144:753)
- After 5 yrs of 70 mg Aln, there substantial residual effect for at least 5 yrs after d/c. So consider d/c Aln after 5 yrs for low-risk pts, and after 10 years for high-risk pts (JAMA 2006;296:2927, Expert Opin Pharmacother 2003;4:1)

Guidelines for treatment of osteoporosis
- First line – Aln -vs others, longer track record, hip fx efficacy, better BMD data, GENERIC+cheap
- Second line – IV zoledronate or SQ denosumab
  - Favor denosumab in patients with CKD
- Third line- raloxifene
  - First line if breast cancer prophylaxis is indicated
- Calcitonin nasal spray has minimal effects on BMD, but may benefit pain slightly
- PTH is usually reserved for patients with severe spine osteoporosis, because of best spine BMD and fracture data, but cumbersome administration.

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Summary (1)
- BMD screening at 65F/70M, sooner if high risk. VFA if 70F/80M, sooner if ht loss >1.5 inches or steroids.
- Rx pts with spine or hip fx, or T-score <-2.5, or osteopenia with >3% 10-yr hip fx risk by FRAX
- Give 1000 units of D, and supplemental ca to achieve TOTAL ca intake of 1000 mg/d.
- Can follow pts on Rx with BMD, mainly to help reinforce compliance

Summary (2)
- First line Rx is usually a PO bisphosphonate (Aln), or IV Zol/SQ Denosumab if intolerant of PO.
- Keep BIS course <5 yrs in low risk patients because of RARE concerns about ONJ or atypical femur fx after 5 yrs
- Can now use SQ denosumab in patients intolerant of oral BIS