OVERVIEW of TREATMENT: WHO and WHEN to TREAT

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UCSF – Osteoporosis: New Insights in Research, Diagnosis, and Clinical Care

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Disclosures: NONE

Diagnostic Assessment – NOF (4/2014): Vertebral Imaging

- Women 70 yrs or > and men 80 yrs or > – if the T-score is ≤ -1.0 (LS, TH, or FN)
- Women 65-69 yrs and men 70-79 yrs – if T-score is ≤ -1.5 (LS, TH, or FN)
- Postmenopausal women and men (age ≥ 50 yrs) with specific risk factors:
  - Low trauma fracture as adult (age 50+)
  - Historical height loss of 1.5 in or > (4 cm)
    - Defined as difference between current height and peak height (age 20)
  - Prospective height loss of 0.8 in or > (2 cm)
    - Defined as difference between current and previously documented heights
  - Recent or ongoing long-term glucocorticoids
- If DXA not avail, then vert imaging may be considered based on age alone
- If stopping therapy (as it could modify that decision)

Selecting Treatment for the Individual Patient

- How high is the risk for the individual (clinical + FRAX)
- What efficacy – trying to achieve
- What risk reduction for which type of fracture is needed
- Adverse event profile of the agent (vs patient) – OK
- What treatment/course of action will patient accept and comply with

Fracture Reduction - PMO

<table>
<thead>
<tr>
<th></th>
<th>Spine</th>
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<tbody>
<tr>
<td>ET/HT</td>
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<td>Zoledronic acid</td>
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<td>Denosumab</td>
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<tr>
<td>Teriparatide</td>
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### Treatment - PMO

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<td>Teriparatide</td>
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</tr>
</tbody>
</table>

*Bazedoxifene/Estrogen – no fracture efficacy, preserves BMD*

### Treatment Options - Men

**Approved for Men**

- Calcitonin
- Alendronate | XX
- Risedronate | XX
- Ibandronate
- Zoledronic acid | XX
- Denosumab | XX
- Teriparatide | XX
- Testosterone | 5(8)

### Considerations – New Starts

- Anti-resorptive: Bisphosphonate, Denosumab, (Raloxifene)
- Anabolic: teriparatide
- eGFR
- Infectious risk
- Hypocalcemia risk
- Concomitant meds
- Active dental issues
- Costs
- Contraindications
- Daily injection hurdle

### Treatment Risks/Benefits

- **Raloxifene**: hot flashes, VTE; no hip/nonvertebral fracture efficacy
- **HT/ET**: WHI
- **Bisphosphonates**: efficacy against all fractures, duration ("FDA guidance" – NEJM 2012, Whittaker et al), AFF, ONJ*, musculoskeletal pain, GI, acute phase response (IV esp)
- **Denosumab**: efficacy against all fractures, infection, AFF, ONJ*

* Stress preventive care

- **Risk Factors:**
  - Age > 65
  - **Periodontitis** - - *get dental clearance before*
  - Prolonged use of BP’s (> 2 years)
  - **Smoking** - - *stop*
  - Denture wearing - - *review w/dentist if ?*
  - Diabetes - - *try for better control, no evidence it changes risk*
  - Corticosteroids +/-
  - EXTRCTIONS – recent or planned
  - Implants – recent or planned

My Approach:  Treatment Naïve Patient

- Gather clinical data, check **FRAX scores** – good place to start talking about relative risk with patient
- Consider PO vs IV bisphos – comparable fracture reduction (except for ibandronate)
- Costs and compliance are different
- PREFER IV bisphos in hip fracture pts (i.e., zol acid) -- trial in that population incl men and women (Lyles K et al, NEJM, 2007)
- Prefer IV bisphos (ZA) or denosumab for patients at high risk for hip fractures or GI absorption is uncertain
- Use denosumab if reduced eGFR

My Approach:  Previously Treated Patient

- What has the patient taken and for how long?
  - Establishing this can be difficult
  - Determining compliance with prescribed med – also difficult
  - KEY - document prior therapy and responses to it (tend to lump the bisphos drugs together – no guidance)
  - Is the patient on a “drug-holiday” and when did it start?
  - What were parameters at start – DXA, BTM, spine xray?
- Does the pt need treatment now or is it OK to wait, observe, get more data?
  - Is there a fracture, loss of BMD exceeding LSC
  - ConsiderRaloxifene after “drug holiday”
- Do I need to do a secondary osteoporosis **workup** or am I satisfied that relevant causes are excluded?

When Teriparatide ?

- **Glucocorticoid-induced osteoporosis**
  - Moderately low to severely low BMD and or fractures
  - “Low turnover state” – teriparatide performs better than ALN in this population
- Patients with severe osteoporosis – **T scores -3.0 to -4.0 range or lower** with (or without) fractures
  - First-line therapy – if possible
  - Improves both mass and microarchitecture
- Patients intolerant to or failed other agents
  - Had a fracture on therapy
- Post-op in atypical femoral fractures*, poorly healing “stress fractures”* (common question)

*off label
DENOSUMAB - Indications (PI-2014)

1. **PMO in women** - “at high risk for fracture”
   
   ("history of osteoporotic frx or multiple risk factors for frx or who have failed or are intolerant to other therapy")

2. **Men on ADT for non-metastatic prostate ca** - at high risk for fracture, to increase bone mass

3. **Men with osteoporosis** – at high risk for fracture, to increase bone mass

4. **Women with breast ca on AI** - at high risk for fracture

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**DENOSUMAB Adverse Drug Effects (PI-2014)**

<table>
<thead>
<tr>
<th></th>
<th>Back pain</th>
<th>Extremity pain</th>
<th>Musculoskeletal pain</th>
<th>Cystitis</th>
<th>Arthralgias</th>
<th>Nasopharyngitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMO (≥ 5%)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Men (≥ 5%)</td>
<td>+</td>
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<tr>
<td>Cancer pts (&gt;10%)</td>
<td>+</td>
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Denosumab: Other Considerations

- Hypocalcemia – contraindication
- Vitamin D deficiency - correct before use
- PI → 400 IU vit D3 and 1000 mg Ca daily

**NO dose adjustment with CKD**

- If creat clearance < 30 ml/min – risk for hypocalcemia substantially greater
- CKD and dialysis pts – monitor Ca, Phos, Mg – hypocalcemia (sometimes serious)
- Marked increases in PTH – may be seen

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**DECIDING - WHO TO TREAT AND WITH WHAT - 3 cases -**
**Case 1**

61 yo Caucasian female lab tech ref for 2\textsuperscript{nd} opinion

- Healthy whole life, regular cycles until menopause at age 51 (2004); began having DXA scans then
- For 5 yrs post-menopause took Estroven\textsuperscript{*}
- Finger FX (age 9), pelvic FX (age 23) in MVA
- No smoking, ETOH, illicit; no height loss, eating disorder
- Exercises 6/7 days, runs 20 miles/week
- Diet: 3 dairy servings/d
- Meds: 500 mg Ca, 2000 IU D3, many herbals

\begin{itemize}
  \item PE: wnl, Ht = 5’4” (162.6 cm) Wt = 115.5 lbs (52.4 kg)
\end{itemize}

\textsuperscript{*}Black Cohosh

**Case 1 - Questions**

61 yo Caucasian female lab tech ref for 2\textsuperscript{nd} opinion

1. Would you do more testing?
2. Would you institute pharmacologic therapy?
3. If yes, what would you choose?
4. If patient takes your advice, when would you repeat DXA?

Using FN T score, 10 yr risk major \( \to \) 11\%, hip \( \to \) 2.2%
Case 2

68 yo Cauc female freelance editor ref for 3rd opinion

- Healthy except for depression her “whole life”, rx’ed with TCA, MAO-I, SSRI’s
- Menopause ~age 50, no symptoms, no HT
- Mostly regular cycles, used OCP’s, no depo-provera
- Smoked ½ ppd – 1 ppw until 6 mos ago (~50 yrs)
- Drank 1-1.5 bottles wine/week (20’s-late 60’s)
- Walks daily, minimal-no dairy intake
- FH: sister - osteopenia, mother – scoliosis; no FRX
- ROS: no frx, falls; states she lost 2” ht (5’8”)
- Meds: Lexapro, Ca 1000 mg/d, vit D3 2000 IU/d

• PE: mild scoliosis, no blue sclerae, cushingoid features Ht=5’ 6 1/4” (168.3 cm) Wt=142.5 lbs (64.6 kg)

LUMBAR SPINE  TOTAL HIP  FEM NECK

<p>| | | | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>3/2012</td>
<td>0.740</td>
<td>0.724</td>
<td>0.611</td>
</tr>
<tr>
<td>Age 66</td>
<td>(-2.8)</td>
<td>(-1.8)</td>
<td>(-2.1)</td>
</tr>
<tr>
<td>8/2013</td>
<td>0.724</td>
<td>0.658</td>
<td>0.571</td>
</tr>
<tr>
<td>Age 67</td>
<td>(-2.9)</td>
<td>(-2.3)</td>
<td>(-2.5)</td>
</tr>
<tr>
<td>% change (17 mos)</td>
<td>-2.1%</td>
<td>-6.5%</td>
<td>-9.1%</td>
</tr>
</tbody>
</table>

(1) Would you recommend pharmacologic therapy?

- 2 MD’s had recommended treatment, pt did not accept rec’s

(2) Would you recommend further workup?
Chart Review/Further Eval

LABS:

2011: 25 OH D  32 ng/ml
2012: chem, LFTs, Ca, alb, CBC, phos, TFTs –nl
2013: chem, Ca, phos, TSH – nl; 25 OH D  40 ng/ml
2014: antigliadin < 10; CBC, SPEP, TSH, PTH (33);
1,25 D (48), 25 OH D  29 ng/ml
24 hr U-Ca (on suppl) → 465 mg
24 hr U-Ca (off suppl) → 340 mg
Serum CTX: 589 pg/ml (40-465)
24 hr U-cortisol: 81 (nl 4-50)
overnight DEX supp test: cortisol 1

FRAX: 10 yr major 21%, hip frx 4.8%

150-250 mg/24 h

Chart Review/Further Eval

LABS:

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overnight DEX supp test: cortisol 1

FRAX: 10 yr major 21%, hip frx 4.8%

T/L spine: diffuse gen osteopenia, multi-level ant vert bodywedging (T-spine); severe “osteoporotic” frx of L3 with 50% height loss

Case 2

(3) What pharmacologic therapy would you recommend?

HT/ET Bisphos (PO, IV) TSEC
Raloxifene Denosumab (CEE+Bazedox)
Calcitonin Teriparatide
**Case 2**
(3) What pharmacologic therapy would you recommend?
- HT/ET
- Bisphos (PO, IV)
- TSEC
- Raloxifene
- Denosumab (CEE+Bazedox)
- Calcitonin
- Teriparatide

(4) Does the elevated U-Ca (off suppl) make TPTD less attractive? (YES)

**DX:** PMO, spinal compression fracture, + h/o smoking, drinking, depression, SSRI, idiopathic hypercalciuria (genetics - may contribute)

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**Case 3**

**80 yo Cauc male referred for low bone mass**
- + HTN, CKD stage 3-4, hyperlipidemia, OSA, BPH, CPPD/OA, hypothyroidism, AAA
- Shoulder xray → "osteopenia" → DXA
- Age 70: seen by Endo → Ca ~11.0, iPTH ~100 and nl eGFR (PHPT); did not f/u, refused surgery & DXA
- c/o 3 yrs of fatigue – can’t work or exercise; no fractures or stones
- Meds: Amlo, vit D3 (1000 IU/d), T4, Losartan, Metop, MVI, Prava, Tamsulosin
- Habits: heavy ETOH 1960’s-80’s, no smoking (45 y)
- Frequent falls – house is on a steep hillside
- FH: neg

PE: OA changes DIP’s 
Ht = 64” (162.6 cm) 
Wt = 129 lbs (58.6 kg)

**LABS:** (4-6/2014)
- S-Ca 10.2, 10.4, 9.6, 9.9 mg/dl
- S-phos 4.0, 3.5, 3.4 mg/dl
- S-creat 2.99, 2.67, 2.4 mg/dl
- eGFR 20’s
- iPTH 126, 143, 122 pg/ml (nl to 65)
- 25 OH D 33 ng/ml
- 1,25 D 13, 22, 26 pg/ml
- Testo 285 ng/ml
- S-CTX 585 pg/ml (87-345)
- BSAP 12 (15-41)

<table>
<thead>
<tr>
<th></th>
<th>L1,L4, Mean</th>
<th>Fem Neck</th>
<th>Total Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>0.771, 0.975, 0.887 (-2.7), (-1.0), (-1.8)</td>
<td>0.515 (-3.1)</td>
<td>0.721 (-2.1)</td>
</tr>
</tbody>
</table>

**FRAX:** 10 yr major op frx 13%, hip 6.9%
Case 3 - Questions

(1) Given the clinical presentation, DXA, FRAX scores, labs, would you treat this patient with pharmacologic therapy to reduce his fracture risk?

(2) What agent would you select?

Treatment Options

Approved for Men

- Calcitonin
- Alendronate
- Risedronate
- Ibandronate
- Zoledronic acid
- Denosumab
- Teriparatide
- Testosterone

(3) What adverse event is he at risk for? How would you manage it?
Denosumab-induced hypocalcemia
Block GA et al, J Bone Miner Res, 2012

- Single dose (60 mg) D-MAB given to 55 pts with varying degrees of renal impairment – followed for ~3 mos
- Ca, vit D supps were NOT originally required but later in study given with dose of D-MAB
- NO one who got Ca and vit D got HYPOCALCEMIC

- 7 pts had [Ca] nadir between 7.5 and 8.0 mg/dL
- 5 pts had [Ca] nadir below 7.5 mg/dL – JUST like this pt (4/5 had advanced CKD)
- 2 required hosp for IV Calcium

Case 3 - Questions

1) Given the clinical presentation, DXA, FRAX scores, labs, would you treat this patient with pharmacologic therapy to reduce his fracture risk?

2) What agent would you select?

3) What adverse event is he at risk for? How would you manage it?

Few days before injection, start Ca supplements (1000 mg/d), calcitriol – continue for 2-3 weeks (mild PHPT)
Check serum [Ca] at day 7, 14, 21
Warn patient of symptoms of hypocalcemia
(Consider) giving ½ dose (30 mg)

~ CONCLUSIONS ~

- Many options for therapy (more coming)
- Goal - treat pts at (substantial) risk for fracture & inform them well
- Many pts are not being treated at present
- Weigh risks and benefits carefully in determining → right drug/duration for the individual patient
ONJ: Executive Summary of Recommendations  
(Hellstein et al, J Am Dent Assoc, 2011)

Recognize that pts on anti-resorptives (bisphos, denosumab) are at risk

INSTITUTE:
- Oral health program
- Sound hygiene practices
- Regular dental care
- NO BTMs – none validated in predicting risk
- ? d/c BP – for dental procedures → NO - may NOT lower risk, but may have negative effects on bone treatment outcomes

ONJ: Executive Summary of Recommendations  
(Hellstein et al, J Am Dent Assoc, 2011)

• Speaking to Dental Providers:
  - Generally NO need to modify routine dental treatments
  - Routine dental exams – recommended
  - If not in routine dental care → do a “comprehensive oral exam” (DENTAL clearance before or early in RX – makes sense to me)
  - Extractions are a risk → minimize bone exposure
  - Implants – reviewed by them - several series (95-100% success, no ARONJ)
  - Many other specific dental mgmt recommendations in report

www.jada.ada.org/content/142/11/1243

Osteonecrosis of Jaw: Executive Summary of Recommendations  
(Hellstein et al, J Am Dent Assoc, 2011)

• BRONJ = BP-related ONJ renamed to ARONJ or anti-resorptive agent-induced ONJ

Conclusions:
“...highest reliable estimate of ARONJ is ~ 0.10%. Osteoporosis is responsible for considerable morbidity and mortality. Therefore, the benefit provided by antiresorptive therapy outweighs the low risk of developing ONJ.”
### Table 4: Exclusion of Secondary Causes of Osteoporosis

<table>
<thead>
<tr>
<th>Blood or serum</th>
<th>Top Non-Hormonal Menopause Treatments</th>
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<tbody>
<tr>
<td>Complete blood count (CBC)</td>
<td><strong>Estroven (Black Cohosh): #10/10</strong></td>
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<tr>
<td>Chemistry levels (Calcium, renal function, phosphorus and magnesium)</td>
<td><strong>Top Non-Hormonal Menopause Treatments</strong></td>
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<tr>
<td>Liver function tests</td>
<td><strong>Estroven (Black Cohosh): #10/10</strong></td>
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<tr>
<td>Thyroid-stimulating hormone (TSH) &lt;7 free T4</td>
<td><strong>Top Non-Hormonal Menopause Treatments</strong></td>
</tr>
<tr>
<td>25(OH)D</td>
<td><strong>Estroven (Black Cohosh): #10/10</strong></td>
</tr>
<tr>
<td>Parathyroid hormone (PTH)</td>
<td><strong>Top Non-Hormonal Menopause Treatments</strong></td>
</tr>
<tr>
<td>Total testosterone and gonadotropin in younger men</td>
<td><strong>Estroven (Black Cohosh): #10/10</strong></td>
</tr>
<tr>
<td>Bone turnover markers</td>
<td><strong>Top Non-Hormonal Menopause Treatments</strong></td>
</tr>
<tr>
<td>Consider in selected patients</td>
<td><strong>Estroven (Black Cohosh): #10/10</strong></td>
</tr>
<tr>
<td>- Serum protein electrophoresis (SPEP), serum immunofixation, serum free light chains</td>
<td><strong>Top Non-Hormonal Menopause Treatments</strong></td>
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<td>- Tissue transglutaminase antibodies (IgA and IgG)</td>
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<td>- Iron and ferritin levels</td>
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<td>- Prostate level</td>
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#### Bone Density Measurements

<table>
<thead>
<tr>
<th>Year</th>
<th>LS (T Score)</th>
<th>Total Hip (T Score)</th>
<th>F Neck (T Score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>0.907 (-1.3)</td>
<td>0.832 (L) (-0.9) 0.857 (R) (-0.7)</td>
<td>0.684 (-1.5) 0.759 (-0.8)</td>
</tr>
<tr>
<td>2008</td>
<td>0.805 (-2.2)</td>
<td>-11.2% 0.774 (L) (-1.4) 0.811 (R) (-1.1)</td>
<td>0.629 (-2.0) 0.719 (-1.2) -8.0% -5.3%</td>
</tr>
<tr>
<td>2011</td>
<td>0.785 (-2.4)</td>
<td>-13.4% 0.730 (L) (-1.7) 0.767 (R) (-1.4)</td>
<td>-12.2% 0.610 (-2.1) 0.857 (-1.7) -10.8% -13.4%</td>
</tr>
<tr>
<td>2013</td>
<td>0.725 (-2.9)</td>
<td>-20% 0.722 (L) (-1.8) 0.772 (R) (-1.4)</td>
<td>-13.2% 0.673 (-2.5) 0.644 (-1.8) -11.1% -15.5%</td>
</tr>
</tbody>
</table>

*Using T Score, 10 yr risk major fracture hip:* 10%