Osteoporosis: Advances in Management - 2016

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Disclosures

• Research Consultation
  – Amgen

• National Bone Health Alliance
  – Co-Chair

• Opinions are those of the speaker and not necessarily those of the U.S. Department of Veterans Affairs
Topics

• Fractures are common
• Many patients not evaluated or treated
• Treatments (Bisphosphonates & Others)
  – Positive Effects
  – Side Effects
  – Non-pharmacologic Rx
• Review of longer term studies
• Individualizing Treatment
Osteoporotic Fx Incidence is High in Postmenopausal women

### Incidence of Chronic Disease: Men

<table>
<thead>
<tr>
<th>Disease</th>
<th>Annual Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer</td>
<td>100,000</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>200,000</td>
</tr>
<tr>
<td>Alzheimer’s Disease</td>
<td>300,000</td>
</tr>
<tr>
<td>Stroke</td>
<td>400,000</td>
</tr>
<tr>
<td>Heart Attack</td>
<td>500,000</td>
</tr>
<tr>
<td>Osteoporotic Fracture</td>
<td>600,000</td>
</tr>
</tbody>
</table>

### References
- Anon, National Osteoporosis Foundation/Fast facts on osteoporosis, 2008
EVERY YEAR, THERE ARE 2 MILLION BONE BREAKS THAT ARE NO ACCIDENT, BUT SIGNS OF OSTEOPOROSIS.
USA: 2 Million OP Fractures/year

- ~1,500,000 Osteoporotic Fractures/Yr in women
- ~500,000 Osteoporotic Fractures/Yr in men
- Osteoporosis Rx →
  - ↓ Vertebral Fracture 41-70%
  - ↓ Non-vertebral fracture 25-39%
  - ↓ Hip fracture 40-51%

Modified from O'Connell & Vondracek Pharmacotherapy
7th Ed, 2008
Fracture Facts

• At age 50:
  – Women: 1/3 lifetime fracture risk
  – Men: 1/5 lifetime fracture risk

• Europe + Americas: ~4.5 million fractures/year

• By 2050:
  – Women: Hip fracture incidence ↑240%
  – Men: Hip fracture incidence ↑310%
Secondary Fracture Prevention: 20% Rule

• After an osteoporotic fracture: risk for a second fracture ~20% in 1 year
• After a hip fracture, ~20% die within 1 year
• Only ~20% of hip fracture patients have attention paid to underlying osteoporosis
• In 1 study, Rx of osteoporosis after hip fracture decreased mortality by >20%.

Secondary OP: Short List

- GIOP (Glucocorticoid-induced)
- Hyperthyroidism
- Hypogonadism
- Malabsorption (e.g. celiac disease)
- Alcohol Excess
- Hypercalciuria
- Hyperparathyroidism
- Hyperprolactinemia
- Aromatase inhibitors, tamoxifen in premenopausal women, ADT in men
Secondary Osteoporosis

• Treatment of underlying disorder may be sufficient to reduce fracture risk
• Treatment will be lifetime in many cases
• Patients will need re-assessment
  – Poor adherence to treatment
  – Development of “garden variety” OP with aging
Treatment of Osteoporosis

- Treatment of Underlying Secondary Causes
- **Bisphosphonates**
- Hormone replacement therapy
- SERMs (Estrogen agonist/antagonists)
- Denosumab
- Teriparatide, PTH (1-84)
- New agents on the way
- Fall risk reduction, calcium/vitamin D
### Bisphosphonates: FDA-Approved Indications

<table>
<thead>
<tr>
<th>Agent</th>
<th>Osteoporosis: Women</th>
<th>Osteoporosis: Men</th>
<th>Glucocorticoid-induced Osteoporosis</th>
<th>Secondary Fracture Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Risedronate</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Ibandronate</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tbody>
</table>
Bisphosphonates

• All approved bisphosphonates reduce spine fracture
• All approved bisphosphonates have side effects
  – Osteonecrosis of the Jaw (ONJ)
  – Atypical Femoral Fractures (AFF)
Oral Alendronate

• **Advantages**
  – Generic (cheap!)
  – Longest experience
  – Long terminal half-life
  – Most long-term data

• **Disadvantages**
  – Concern about generics
  – Long terminal half-life
  – Most ONJ and AFF with alendronate
Oral Risedronate

• Advantages
  – Monthly dose available
  – Shorter terminal half-life
  – Long experience
  – New post-breakfast pill
  – Possible better GI tolerance
  – Generic becoming available (weekly & monthly)

• Disadvantages
  – Less long term data
  – Shorter terminal half-life
  – All bisphosphonates are associated with ONJ and AFF
Oral Ibandronate

• **Advantages**
  - Monthly dose
  - Good U.S. advertising has increased interest in osteoporosis
  - Hip fracture risk reduction in post-hoc study of high risk patients
  - Generic version becoming available

• **Disadvantages**
  - No hip fracture risk reduction overall
  - Less long term data
  - All bisphosphonates are associated with ONJ and AFF
Intravenous Zoledronic Acid

**Advantages**
- Dose studied is dose given (5 mg i.v.)
- ↓ Subsequent fracture in hip fracture patients
- ↓ Mortality in hip fracture patients
- Convenient annual dosing
- May be able to ↑ interval between doses
- Generic becoming available

**Disadvantages**
- Acute phase reaction with first dose
- More expensive
- Requires infusion center or trained personnel
- All bisphosphonates associated with ONJ and AFF
Bisphosphonates:
Vertebral Fracture Reduction

zoledronic acid [8]
etidronate [9]
ibandronate [10]
alendronate [11-13]
alendronate pooled
risedronate [14-15]
risedronate pooled

Relative Risk

JP Jansen Semin Arthritis Rheum
40:275, 2011
Bisphosphonates: Hip Fracture Reduction
Bisphosphonates: Non-hip, Non-vert Fx Reduction

zoledronic acid [8]
etidronate [9]
ibandronate [10]
alendronate [11-13]
alendronate pooled
risedronate [14-15]
risedronate pooled

Relative Risk

0.00 0.20 0.40 0.60 0.80 1.00 1.20 1.40 1.60 1.80 2.00
Bisphosphonates in Practice: Dilemmas Facing the Clinician

• Millions with osteoporosis & ↑fracture risk
• Bisphosphonates decrease fracture risk
• **Rx is for years; optimal length of Rx is unknown**
• Highly publicized side effects:
  – Who will get them?
  – Concern for side effects → ↓ adherence
  – Minority of women with PMOP are treated
  – Even fewer men are evaluated/treated for OP

Nonadherence

• Must take 75-80% of Rx in order to show ↓fracture
  – ~50% of patients still on Rx at 1 year
• Reasons for poor adherence
  – No symptoms: osteoporosis is silent until fracture
  – Complex dosing regimens
  – Cost no longer a problem
  – Concern about side effects

Compliance and Fractures

FIGURE 2. Probability of fracture in 24 months in the bisphosphonate-treated patients. MPR = medication possession ratio.

Side Effects: Mild, Avoidable, or Rare

- **GERD**: take Rx correctly, have GERD under control first
  - Avoid oral Rx in esophageal mobility disorders
- **Acute Phase Reaction**: mostly with first IV dose; hydration and acetaminophen help
- **Hypocalcemia**: unusual but assure adequate calcium and vitamin D
- **Inflammatory Eye Disease** – uveitis, rare.
Esophageal Cancer & Oral Bisphosphonates

- UK: ↑Risk 1.30 (1.02-166), higher with longer Rx
- UK: No ↑Risk 1.07 (0.77-1.49)
- Probably no ↑ risk in years 1-3
- 5 extra cases/10,000 pt-yrs in years 4-7
- **Recent meta-analysis: No increased risk**
- Risk factors for osteoporosis AND esophageal ca:
  - Age
  - Alcohol excess
  - Smoking

Dixon & Solomon Nat Rev Rheum 7:369, 2011;
K Sun, Osteoporos Int 24:279, 2013
Osteonecrosis of the Jaw (ONJ)

- More common in cancer patients on high dose/high frequency I.V. bisphosphonates
- Exposed bone, poor healing after extraction
- Probably between 1/10,000-1/100,000 in osteoporosis doses
- Mechanism still unclear, probably multi-factorial
- Poor general dental status → ↑risk

S. Khosla, J Bone Miner Res
22:1479, 2007
American Dental Association Recommendations

- Attention to teeth before Rx
- Good dental hygiene for all
- Avoid invasive dental procedures if possible
- No need to stop Rx if procedures needed
- Worst case incidence: 1/1,000
- ADA prefers term ARONJ: Anti-resorptive associated osteonecrosis of the jaw

J Hellstein, JADA 142:1243, 2011
Atypical Subtrochanteric Fractures

- Unusual
- Mechanism unclear
- Need to know background incidence – are osteoporosis patients at ↑risk before Rx?
- Probably 5 cases/10,000 patient-years
- Probably 30-100 typical fractures prevented for every atypical fracture
- Likely related to duration of bisphosphonate Rx

E Shane, JBMR 25:2267, 2010; 29:1, 2014
J Schilcher NEJM 364:1728, 2011
P Vestergaard, OI 22:993, 2011
Atypical Femoral Fracture

E Shane J Bone Miner Res 25:2267, 2010
Long Term Bisphosphonate Studies

• FLEX- 5 years of alendronate – then randomized to alendronate or placebo for 5 more years
• HORIZON – 3 years of zoledronic acid – then randomized to ZA or placebo for 3 more years – Second extension for Z6 subjects

DM Black JAMA 27:2927, 2006;
Design of Fracture Intervention Trial (FIT)  
Long-term Extension (FLEX) Trial

6459 Participants randomized

FIT (3-4.5 yrs)

3223 Assigned to receive PBO
3236 Assigned to receive ALN

Post-FIT ALN open label (1-2 yrs)

2857 Eligible for FLEX screening

FLEX (5 yrs) PBO or ALN 5/10 mg

1099 FLEX Participants Randomized

437 Assigned to PBO
662 Assigned to ALN 5 or 10 mg

B McNabb J Bone Miner Res 28:1319, 2013  
Effects of ALN for 7 Years

Tonino, JCEM. 85:3109, 2000
Total Hip BMD: Mean % Change from FIT Baseline

Mean Percent Change

Year

FIT

F 0 F 1 F 2 F 3 F 4 FL 0 FL 1 FL 2 FL 3 FL 4 FL 5

FLEX

FIT

F 0 F 1 F 2 F 3 F 4 FL 0 FL 1 FL 2 FL 3 FL 4 FL 5

Mean Percent Change

0 1 2 3 4 5

P<0.001 ALN vs PBO

= Placebo

= ALN (Pooled 5 mg and 10 mg groups)
Design of HORIZON EXTENSION

7736 Participants randomized to Tmt

3876 Received PBO
3867 received ZLN 5mg (0,12,24 months)

ZLN or PBO for 3 yrs

One YR Post-Horizon

EXTENSION ZLN or PBO for 3 years

1233 Participants Randomized

617 to PBO- Z3P3
616 ZLN 5 mg/YR for 3 YRS Z6

DM Black NEJM 356:1809, 2007
DM Black JAMA 174:1126, 2012
F Cosman J Clin Endocrinol Metab 99:4546, 2014
BMD – Zoledronic Acid

Mean % Change from Baseline

Re-Randomization

FEMORAL NECK

LUMBAR SPINE
Summary of Vertebral Fracture Reductions for FLEX and HORIZON

Relative Risk (Bis vs. PBO)

Bisphosphonate benefit

Slide Courtesy of Dr Dennis Black
Summary of FLEX and Horizon Extension Studies
LONG TERM BP vs SWITCH to PBO

• FLEX demonstrates that ALN 10 yrs
  – Maintained BMD at all sites versus loss in PBO, p<0.001
  – Reduced risk of clinical vertebral fractures: RR=0.45 (0.24-0.85)

• HORIZON extension demonstrates that ZLN for 6 yrs
  – Maintained BMD at all sites versus loss in PBO, p<0.001
  – Reduced risk of morphometric vertebral fractures: RR=0.51 (0.26,0.95).

DM Black JAMA 296:2927, 2006
% Change TH BMD: 6 vs. 9 years of ZA

DM Black, J Bone Miner Res 30:934, 2015
Long Term Studies

- Numbers are small
- Alendronate: Benefit appears to be in those still at high risk after original study (3-5 years)
- Probably some residual benefit in year or two after stopping bisphosphonate
- Does $\Delta$ BMD with time imply $\Delta$ Fracture Risk?
- Fracture reduction versus side effects

AV Schwartz JBMR 25:976, 2010
BL McNabb JBMR 28:1319, 2013
Bisphosphonate Drug Holiday

• Drug Holiday:
  – Data are sparse
  – Holiday: Maintenance of BMD at the spine and loss in hip: is it clinically significant?

  – Remaining Questions
    • Who is a candidate?
    • What factors should be considered?
    • Who should resume therapy and when?
    • Should we switch to another therapy?
    • How to follow patients?
How long do BP effects last?

One Dose of ZA suppresses BTMs for 3 years

A Grey, J Bone Miner Res 25:2251, 2010
Duration of NTx Suppression in Men

DA Johnson, Endocr Pract 16:960, 2010
Effect of ZA on BMD

One dose of ZA may have an effect on BMD for 2+ years

A. Grey J Bone Miner Res 25:2251, 2010
Legacy Effects

• What happens after stopping a treatment?
• Do the benefits continue?
• Do risks subside?
Intensive treatment mean 8.2% vs. 8.0% for Conventional treatment.

DCCT/EDIC Intervention Study Year

DCCT Intervention

Training

EDIC Observation

Glycosylated Hemoglobin (%)

0 1 2 3 4 5 6 7 8 9 10

0 1 2 3 4 5 6 7 8 9 10

DCCT Research Group. NEJM 329:986, 1993
DCCT/EDIC. JAMA 290:2159, 2003
DCCT/EDIC: Cardiovascular Events

Risk reduction 42\% (P=0.016)

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>Intensive</th>
<th>Conventional</th>
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<tr>
<td>Years From Study Entry</td>
<td>705</td>
<td>683</td>
</tr>
<tr>
<td>1</td>
<td>683</td>
<td>629</td>
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<tr>
<td>2</td>
<td>629</td>
<td>113</td>
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<tr>
<td>3</td>
<td>113</td>
<td>92</td>
</tr>
</tbody>
</table>

DCCT/EDIC Study Research Group NEJM 353:2643, 2005
Legacy Effect of ALN at Year 9

Effect of 2, 4, or 6 years of 2.5-10 mg/d of ALN.

Effect of 20 mg/d of ALN for 2 years.

YZ Bagger, Bone 33:301, 2003
Duration of Bisphosphonate Rx

• 5 years of oral Rx for high fracture risk
  – Spread out i.v. zoledronic acid ?q 18-20 months?

• At 3-5 years, assess fracture risk again
  – DXA (T < -2.5), history of fracture
  – Side effects – risks predictable?
  – Other factors
    • Meds (e.g. continuing glucocorticoids, ADT, Aromatase Inhib)
    • Falling and frailty
    • Competing causes of mortality

• Assess again periodically

RA Adler J Bone Miner Res 31:16, 2016; RA Adler Endocrine 2016
Bisphosphonates: ↓Mortality

- IV-Post-hip fracture: 28% ↓relative risk
- PO-Post-hip fracture: ~63% ↓relative risk/year of Rx
- Dubbo Trial: ↓Mortality in women, possibly in men
- Institutionalized elders: HR [0.73 (0.56-0.940)]

- Legacy effects apply only to bisphosphonates!

Lyles, NEJM 357:1799, 2007;
Beaupre OI 22:983, 2011;
Center JCEM 96:1006, 2011;
Sambrook OI 22:2551, 2011
Osteoporosis Rx: Other Agents

- HRT – Prevention Only
- SERMs: Raloxifene and Bazedoxifene
- Denosumab – Anti-RANKL Ab
- Calcitonin – Third (4th?) line agent
- Strontium Ranelate – Europe/Australia
- Teriparatide – Only Anabolic Available
- No Legacy Effect with any of these agents!
HRT and Osteoporosis

- Estrogens are FDA approved for osteoporosis prevention only.
- Not approved for treatment.
- WHI: HRT lowers hip fracture risk.
- HRT: Quick decrease in bone after discontinuation.
- Not a primary use of HRT.
- Bazedoxifene/estrogen combination.
SERMs: Raloxifene

• Estrogen agonist/antagonist
• +Estrogen effect on bone
• Daily oral administration
Raloxifene Side Effects

- ↑VTE: Pulmonary Embolism, retinal vein
- ↑CVA Death
- ↑Hot flashes
- Leg cramps
- Peripheral edema
- Arthralgias/myalgias
Raloxifene for PMO

- **Advantages**
  - Not a bisphosphonate
  - ↓Spine fractures
  - ↓Breast cancer risk
  - Not associated with ONJ or AFF

- **Disadvantages**
  - No ↓hip fracture risk
  - ↑Thromboembolic risk
  - ↑Vasomotor symptoms
Bazedoxifene and Fracture Risk

S. Palacios, Menopause 22:806, 2015
Bazedoxifene

- In U.S. bazedoxifene is available only with conjugated estrogens
- FDA-approved to prevent osteoporosis
- Potential choice for postmenopausal women with uterus and vasomotor symptoms
- Concerns about long term HRT
- Expensive

JV Pinkerton J Clin Endocrinol Metab 99:E189, 2014
BAZ/CE and Spine BMD in 1 year

JV Pinkerton, J Clin Endocrinol Metab 99:E189, 2014
Denosumab for Osteoporosis

- Increases spine and hip BMD (and radius)
- Decreases spine and hip fracture
- Humanized monoclonal antibody
- Greater increase of BMD than alendronate in head to head trial

Denosumab 8 Year Phase 2 Data

Spine BMD Increase (%)

Year 1: 4%
Year 2: 6%
Year 3: 8%
Year 4: 10%
Year 5: 12%
Year 6: 14%
Year 7: 16%
Year 8: 18%

Long Term Study of Denosumab

• 8 yr. BMD: Spine ↑18.4%; Total Hip ↑8.3%
• No increase in side effects
• No increase in Atypical Femoral Fractures
• Continued low typical fracture risk
• Still, a small study, placebo controlled up to 3 years only.

S Papapoulos, Osteoporos Int 26:2773, 2015
Denosumab Side Effects

- Hypocalcemia
- Serious skin infections
- Rashes, eczema
- Bone/joint pain
- Osteonecrosis of the jaw (ONJ)
- Atypical Femoral Fractures (AFF)
SubQ Denosumab

• Advantages
  – Subcutaneous injection every 6 months
  – May be more potent than bisphosphonates
  – Increases radius BMD
  – May continue effect for extended period of Rx
  – Dose studied is the dose used

• Disadvantages
  – Less experience
  – Quick “off”
  – Possible side effect of increased infection
  – Expense
  – ONJ and AFF have been reported
Teriparatide

• PTH (1-34)
• Anabolic
• Increases spine and hip bmd
• Decreases spine and hip fracture
• Different side effect profile
• Works well in GIOP with high fracture risk

KG Saag, Arthritis Rheum 60:3346, 2009
Teriparatide Side Effects

- Nausea
- Dizziness
- Leg Cramps
- ↑Serum calcium 4-6 hours post dose
- No evidence of ↑osteosarcoma at 7 years of 15 year surveillance study

C Capriani J Bone Miner Res 27:2419, 2012
SubQ Teriparatide

• Advantages
  – Increases BMD well
  – Anabolic effect
  – “Natural”
  – Generally well tolerated
  – May decrease back pain
  – May speed fracture healing
  – Not associated with ONJ or AFF (may treat them!)

• Disadvantages
  – Daily subcutaneous injection
  – Can only be used for 2 years
  – Expensive
Strontium

• Strontium Ranelate is approved for osteoporosis in Europe and Australia
• Increases bone density, decreases fracture
• Concerns: cardiovascular risk, skin reactions
• In U.S. patients are getting Strontium Citrate at supplement stores
  – Effective? Dose?
  – Safe?
Rx Duration: Other Agents

• Denosumab
  – Appears to increase BMD up to 10 years
  – Long term: must continue Rx

• SERMs = Estrogen agonist/antagonists
  – Raloxifene not associated with AFF, ONJ
  – Bone loss when Rx stopped

• Calcitonin – less potent & less long term data

• Teriparatide
  – FDA-approved treatment for only 2 years
  – Would be off-label for > 2 yr. lifetime use
Non-Pharmacologic Rx

• Attain Maximal Skeletal Growth
• Calcium + Vitamin D $\rightarrow$ ↓Fracture Risk
• Fall Risk Reduction
  – Improved lower body muscle strength
    • Tai chi, yoga, weight-bearing exercise
  – Good vision
  – Walking aids
  – Home safety

CM Weaver, Osteoporos Int 27: 367, 2016
Potential New Drugs – Not Yet FDA-Approved

- Odanacatib – different anti-resorptive
- Abaloparatide – PTHrP analog, anabolic
- Romosozumab – Anti-sclerostin Ab, anabolic
- Sequential therapy: anabolics and anti-resorptives???

Rx of Osteoporosis: Conclusions

• We will never have all the data needed

• **Patients need periodic individual assessment**
  – Hx/PE, DXA (same machine), ?FRAX
  – What is their true fracture risk?
  – Do benefits outweigh risks?
  – New fracture surrogates needed

• **Hope with new meds**
  – Will sequential Rx work? New anabolics?
  – New fracture surrogates to get new drugs sooner?