Diagnosis and Treatment of Osteoporosis: What's New and Controversial in 2019?

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No Disclosures

What’s New in Osteoporosis

• The “crisis” in treatment and compliance
• Better risk identification and stratification
• New potential concerns about treatments
• When to start and stop bisphosphonates
• Rational use of newer drugs
New York Time June 1, 2016

Fearing Drugs' Rare Side Effects, Millions Take Their Chances With Osteoporosis

By GINA KOLOTA JUNE 1, 2016


A Clear Example of the Therapeutic Gap: Post-Hip Fracture Treatment

- 97,000 commercially insured hip fracture patients, 2004-15 OP
- OP med use 6 mo. after surgery
- Discouraging results: 10% use in 2004 and 3% in 2015...
- Post-op zoledronic acid reduces fractures and mortality!

Desai, Jama Open. 2018; Lyles, NEJM. 2007

Under Recognition and Inadequate Treatment of Osteoporosis

- Among women with fracture or BMD<-2.5 about a third are evaluated and treated...
- Ask about fracture history, note vertebral fractures, use chart reminders for DXA
- One easy fix: identify all hip and vertebral fractures in your practice and treat if appropriate!

Soloman, Mayo Clin Proc, 2005
Shibli-Rahhal, Osteo Internat, 2011
A Quick Review: Risk Factors for Fracture

- The Big Three: older age, postmenopausal female, and Caucasian/Asian

- Other important risk factors
  - Family history of fracture (hip)
  - Low body weight (<127# in women)
  - Smoker, 3 or more drinks/d
  - Certain drugs (steroids, AIs) and diseases (RA, sprue)
  - Previous fracture (especially hip or spine)

- Low bone mineral density (BMD)
  - T-score above -1=normal, below -2.5=osteoporosis

http://www.shef.ac.uk/FRAX/tool.jsp

Calculating Absolute Fracture Risk: FRAX
Who Should Be Tested and Treated?

NOF and ACP Practice Guidelines

- Preventive measures for everyone: adequate calcium/vitamin D, exercise, avoid bad habits
- Screening hip BMD: women >65 (or >50 with risk factors), anyone >50 after fracture, men >70*
- If >70, consider vertebral assessment (DXA VFA)*
- Recommended pharmacologic treatment thresholds:
  - Anyone with hip or spine fracture
  - T-score (any site) < -2.5
  - T-score -2.5 to -1 and a FRAX 10 yr risk >3% hip or >20% major fractures*

*Not endorsed by ACP Guidelines
Non-Drug Therapy To Prevent Osteoporosis?

Non-pharmacologic Interventions: Do Not Underestimate Benefits

- Smoking cessation, avoid alcohol abuse
- Physical activity: modest transient effect on BMD but reduced fracture risk
- Hip protector pads effective (but poor compliance even in nursing homes…)
- Fall prevention: targeted PT, stop sedating meds
  - RCT: home based PT reduced falls by 36%

Liu-Ambrose, JAMA 2019
Calcium and Vitamin D

- Chapuy, 1992
  - Elderly women in long-term care
  - 30% decrease in hip fracture
- Porthouse, 2005:
  - Women >70 with 1+ risk factor
  - No benefit on hip, non-spine (RR=1.0, CI: 0.7, 1.4)
- USPSTF meta-analysis: 11% fewer fractures (together not alone)

How Much Is Enough? The IOM Report

- Calcium (elemental)
  - 1200 mg/d for women >50 and men >70; no more than 2500 mg/d
  - Dietary sources preferred (estimate intake using 300 mg/d plus 300-400 per dairy serving)
  - Supplement use: nephrolithiasis but not CVD
- Vitamin D (non-skeletal benefits not established)
  - 600-800 IU/d (maximum 4,000/d)
  - Recommends serum levels 20-50 ng/ml

Institute of Medicine Report, 2010
Bisphosphonates: What Is Known

- Four approved generic agents in US: alendronate, risedronate, ibandronate, and IV zoledronic acid
  - No head-to-head fracture studies; network meta-analysis show similar efficacy
- New vertebral fracture reduced 50-60%
- Non-spine fractures (including hip) reduced 30-50% if
  - Existing vertebral fracture OR
  - Low hip BMD (T-score < -2.5)
- NNT for 3 yr: 9 for vertebral, 90 for non-spine fracture

Black and Rosen, NEJM 2016

Bisphosphonates: What Is Known and What is Uncertain

- After hip fracture: 40% reduction in non-spine fracture (and mortality) with IV zoledronic acid
  - Similar effect regardless of BMD
  - NNT for 3 yr: 19 to prevent one non-spine fracture
- Efficacy if no hip or vertebral fracture but T < -2.5?
  - Trial evidence that oral alendronate and risedronate do not prevent non-spine fracture...

Lyles, NEJM 2007
Cummings, Jama 1998
McClung, NEJM 2001
Effect of Alendronate on Non-spine Fracture Depends on Baseline BMD

Baseline hip BMD

<table>
<thead>
<tr>
<th>Baseline BMD</th>
<th>Relative Hazard (± 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T -1.5 — -2.0</td>
<td>1.06 (0.77, 1.46)</td>
</tr>
<tr>
<td>T -2.0 — -2.5</td>
<td>0.97 (0.72, 1.29)</td>
</tr>
<tr>
<td>T &lt; -2.5</td>
<td>0.69 (0.53, 0.88)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.86 (0.73, 1.01)</td>
</tr>
</tbody>
</table>

Cummings, Jama 1998

RCTs of Women with Osteopenia? Just One (Zoledronic Acid)

- 2000 women >65, hip BMD -1 to -2.5 and no previous fracture
- Randomized to ZOL or placebo for 6 yr
- 34% fewer non-spine
  - 55% fewer vertebral
  - 35% fewer hip
- NNT for 6 years: 15

Reid, NEJM 2018
More Bad News for Oral Bisphosphonate: Poor Compliance

- 50-60% persistence after one year
- Reasons for non-compliance?
  - Burdensome oral administration (fasting, remain upright for 30 minutes)
  - Upset stomach and heartburn can occur
  - Newer concerns about serious side effects
- Good news: Asking about side effects and positive reinforcement increases oral med compliance by 59%

Clowes, JCEM, 2004

Recent Concerns about Potent Bisphosphonates
**Osteonecrosis of the Jaw**

- Associated with potent bisphosphonate use:
  - 94% treated with IV bisphosphonates
  - 4% of cases have OP, most have cancer
  - 60% caused by tooth extraction. Other risk factors unknown. Infection?

  - Key points: extremely rare, early identification, conservative tx

  - Dental exam recommended before Rx, but no need to stop for dental procedures

  Khan, JBMR 2015
  ADA Guidelines, 2011

**Other Things to Worry About**

- Atrial fibrillation (zoledronate acid and alendronate RCTs)
  - No association in other trials
  - Likely spurious

- Esophageal cancer
  - Case series (FDA author) and two conflicting cohorts,
  - Might be spurious

- Subtrochantic fracture (with atypical features)
  - Undoubtedly real…
**Atypical Femoral Fractures (AFF)**

- Thousands of reports in long-term bisphosphonate users (and others)
- Transverse not spiral, cortical thickening, minimal trauma
- Often bilateral, prodromal pain, abn. imaging (x-ray, bone scan/MR)
- Over-suppression stress fractures?
- Other risk factors? (steroids, RA, DM, Asian...)

ASBMR Task Force, JBMR 2013

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**3 Critical Unknowns About AFFs**

- Mechanism and real relationship with BP use?
  - RR for BP user vary from 2 to >40
  - NNTH: Treat 800-43,000 for 3 yr to cause 1 AFF
- Does treatment duration matter?
  - AFF risk increases after 5-8 years of use
- Risk after stopping?
  - After 1 yr, AFF risk fell 70% in Sweden...

Black et al, NEJM, 2016
Schilcher et al, NEJM 2011, 2014
How Long to Treat with Bisphosphonates?

- Depends upon duration of benefits after stopping

FIT Long-term Extension (FLEX) study
  - Treated with weekly ALN for 5 yr. (N=1099)
  - Re-randomized to ALN or PBO for 5 yr.

Horizon Extension
  - Treated with annual ZOL for 3 yr. (N= 1233)
  - Re-randomized to ZOL or PBO for 3 yr.

Black et al, Jama 2006; Black et al, JBMR 2012

Fracture Risk During FLEX

<table>
<thead>
<tr>
<th></th>
<th>PBO (n=437)</th>
<th>ALN (n=662)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-spine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-vertebral</td>
<td>20%</td>
<td>19%</td>
<td>1.0 (0.8, 1.4)</td>
</tr>
<tr>
<td>Hip</td>
<td>3%</td>
<td>3%</td>
<td>1.1 (0.5, 2.3)</td>
</tr>
<tr>
<td>Vertebral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphometric</td>
<td>11%</td>
<td>10%</td>
<td>0.9 (0.6, 1.2)</td>
</tr>
<tr>
<td>Clinical</td>
<td>5%</td>
<td>2%</td>
<td>0.5 (0.2, 0.8)</td>
</tr>
</tbody>
</table>

Similar results with ZOL in Horizon Extension....
Guidance for Drug Holidays?

• American College of Physicians
  – Stop after 5 yr of bisphosphonate

• National Osteoporosis Foundation (NOF)
  – Consider stopping after 5 yr if “low risk”

• ASBMR Task Force
  – Algorithm with fracture risk factors + BMD


Post-menopausal women treated with oral (≥5 yrs) or IV (≥ 3 yrs) BPs

Hip, spine or multiple other osteoporotic fractures before or during therapy

Yes

Reassess benefits/risks
Consider continue BP (1) or change to alternative therapy (2)
Reassess every 2-3 years

No

Hip BMD T-Score ≤ -2.5 (3)
OR
high fracture risk (4)

Yes

Reassess benefits/risks
Consider continue BP for up to 10 yrs (1)
or change to alternative therapy (2)
Reassess every 2-3 years

No

Consider drug holiday
Reassess every 2-3 years (1)

ASBMR Task Force on Long-Term Bisphosphonate Use, JBMR 2015
Monitoring Drug Holidays

- No specific guidance on duration or monitoring
- How to assess?
  - Repeat BMD might be helpful after 3-5 years (FLEX), but not sooner.
  - Calculate FRAX? No studies
- No data or consensus about re-initiation of anti-resorptive agents or use of newer agents...

Bauer JBMR, 2017; Adler JBMR, 2016

2018 Summary: Who Should Be Treated and When to Stop?

- US treatment guidelines:
  - Existing hip or vertebral fracture? Yes!
  - T-score < -2.5? Yes!
  - “Low bone mass” + FRAX score that exceeds absolute threshold? Oral BPs may not work
- Drug holiday after 5 yr of bisphosphonate? Maybe
  - No hip/vertebral fracture; no fracture on therapy
  - BMD T-score > -2.5 before stopping
  - How long? Monitor? Risk stratify after 3-5 yr
Other Anti-resorptive Agents

• Some clearly less effective than bisphosphonates
  – Calcitonin (poor quality studies)
  – Raloxifene (prevents vertebral fractures only; breast cancer prevention?)
• Denosumab (antibody to RANKL) similar to BPs
  – SQ q 6 months, not cleared by kidneys
  – Expensive, rebound fractures after stopping
  – Both ONJ and AFF reported

The Future: Anabolic Agents

• Most treatments inhibit bone resorption > formation
• Anabolic agents (anabolic steroids, fluoride, intermittent PTH, abaloparatide) stimulate formation > resorption
• SQ PTH (1-34) or al-baloparatide for 18 mo. reduces vertebral and non-spine fracture. No hip fracture data
• After anabolic use bisphosphonate for maintenance
• Expensive, self-administered injections...
  – Use with severe OP, when other agents have failed?

Neer, NEJM, 2001
Miller, Jama, 2016
New and Controversial: Romososumab (Sclerostin Antibody Inhibition)

- Anabolic + Anti-resorptive = Dramatic Effects on BMD
- ARCH: RCT of 4393 postmenopausal women with low BMD and vertebral fractures
- Monthly SQ romososumab vs. oral alendronate for 12 mo, then open label ALN for 12 mo
- After 24 mo: 48% fewer vert fx, 38% fewer hip fx
- BUT more CVD in romo group (2.5% vs 1.9%) so Black Box Warning; ONJ and AFF reported; cost

Saag, NEJM 2017

Osteoporosis 2019 Conclusions

- Treatment rates are low and are dropping rapidly...
- Screening and appropriate treatment = fewer fractures
  - Particularly important for secondary prevention
  - Find and treat patients after hip fracture!
- Bisphosphonates: remain treatment of choice
  - Use when spine/hip fracture or T<-2.5. >-2.5?
  - Adherence counseling. Consider yearly dosing
  - Duration of therapy: 3-5 years then off for many
- Denosumab, anabolics and sclerostin antibody effective but less clear when to use. Pipeline is empty...
Thanks for Listening
Questions or Comments?