Controversies in Osteoporosis Management

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Conflict of Interest

I am disclosing financial relationships as follows:
Global Advisory Boards: Amgen, Radius Health
Honorarium for speaking: Amgen, Radius Health

Michael McClung, MD 2018

Learning Objectives

Attendees at this lecture will
a. appreciate the benefit:risk profile of long-term osteoporosis treatments
b. understand when an osteoporosis “drug holiday” is appropriate
c. review the circumstances where combination therapy is indicated
Osteoporosis

Definition:
A disorder due to bone loss that damages skeletal architecture, weakens the skeleton and predisposes a patient to fracture

• Several osteoporosis drugs effectively and quickly reduce fracture risk in patients with osteoporosis
• Osteoporosis is a chronic disease requiring prolonged treatment
• It is important to develop a strategy for long-term management
• ACP Guidelines – 2017: Treat for only 5 years

Osteoporosis Therapy

• ACP recommends that patients with osteoporosis be treated for 5 years – without monitoring

Recommendation 2: ACP recommends that clinicians treat osteoporotic women with pharmacologic therapy for 5 years.
(Grade: weak recommendation; low-quality evidence)

Recommendation 4: ACP recommends against bone density monitoring during the 5-year pharmacologic treatment period for osteoporosis in women.
(Grade: weak recommendation; low-quality evidence)

Case

• 70 year old woman was diagnosed with osteoporosis
• 1 year earlier, she had experienced a Colles fracture when she fell while hiking
• BMD T-score: lumbar spine -2.0; total hip -3.0; femoral neck -2.8

FRAX
Osteoporosis: Long-term Treatment Plan

- Raloxifene
  - When concerned about hip fracture
- Bisphosphonate
  - After 12-24 months
- Teriparatide
  - After 12-24 months
- Denosumab

**OBJECTIVES**
1. Improve bone strength
2. Reduce risk of fracture
3. Prevent rapid bone loss (less commonly)

**BENEFITS**
1. Effective protection from fractures
   - Vertebral fracture by 50-70%
   - Hip fracture by 40-50%
   - Non-vertebral fracture by 20-25%
2. In general are well tolerated
3. In clinical trials, have a favorable safety profile

**Long-term Osteoporosis Therapy**

**Bisphosphonates and denosumab**

- Fracture protection
  - Begins within months of starting therapy
  - Continues with long-term therapy
  - Wanes when treatment is stopped

**References**
Zoledronic Acid
Onset of Fracture Protection

Vertebral and hip fracture protection occurs within first year of therapy

- Radiographic vertebral fracture
- Hip fracture

**Zoledronic acid**

- **Denosumab**

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Vertebral Fractures with Zoledronic Acid

- Years 1-3
  - P = <0.001
  - % Patients: 3.3% (50/1522)

- Years 4-6
  - Fracture protection persists with long term therapy
  - % Patients: 3.3% (50/1522)

- Years 7-8
  - % Patients: 3.5% (164/489)

- Years 9-11
  - % Patients: 4.4% (158)

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Long-term Denosumab Therapy
Vertebral and Non-vertebral Fractures

- Persistent reduction in fracture risk
Osteoporosis Therapies

Fracture protection
• begins within months of starting therapy
• persists with long-term therapy
• wanes when treatment is stopped
  – even with bisphosphonates

Black DM et al. JAMA 2006;296:2927-38

Cumulative Incidence of Fractures (%)

Years Since FIT

ALN 5 years → Placebo 5 years
Aldronate 10 years

5.4%

2.5%

P = 0.013

2.5%


Osteoporosis Therapies

Long-term Osteoporosis Therapy

Bisphosphonates and denosumab

Fracture protection
• begins within months of starting therapy
• continues with long-term therapy
• wanes when treatment is stopped

Long-term safety
• bisphosphonates: atypical femoral fracture incidence: ~1/1000 after 8-10 years of therapy
• denosumab: over 10 years, no adverse events increased in frequency with long-term therapy

Dell RM et al. J Bone Miner Res 2012;27:2544-50

Dell RM et al. J Bone Miner Res 2012;27:2544-50

Benefits vs Risks of Long-term Bisphosphonate Therapy

Events per 1000 patients

Clinical fractures prevented
Hip fractures prevented
Death prevented
Atypical femoral fractures

Years of bisphosphonate therapy

Modelled after data from:
Cummings SR et al. JAMA 1998;280:2077–82
Dell RM et al. J Bone Miner Res 2012;27:2544-50
No adverse events increased in frequency with long-term therapy

Denosumab: Long-term Safety

Exposure-adjusted Subject Incidence of Adverse Events
(Rates per 100 Subject-years)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 3883)</th>
<th>Cross-over Denosumab (N = 2206)</th>
<th>Long-term Denosumab (N = 2343)</th>
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</thead>
<tbody>
<tr>
<td>All AEs</td>
<td>156.1</td>
<td>96.8</td>
<td>97.0</td>
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<tr>
<td>Infections</td>
<td>39.7</td>
<td>20.7</td>
<td>19.9</td>
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<tr>
<td>Malignancies</td>
<td>1.6</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Eczema</td>
<td>0.6</td>
<td>0.9</td>
<td>0.9</td>
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<tr>
<td>Hypocalcemia</td>
<td>&lt; 0.1</td>
<td>&lt; 0.1</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0.1</td>
<td>&lt; 0.1</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>19.4</td>
<td>10.1</td>
<td>10.3</td>
</tr>
<tr>
<td>Infections</td>
<td>1.3</td>
<td>1.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Cellulitis or erysipelas</td>
<td>&lt; 0.1</td>
<td>&lt; 0.1</td>
<td>&lt; 0.1</td>
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<tr>
<td>Fetal AEs</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw</td>
<td>0</td>
<td>&lt; 0.1</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Atypical femoral fracture</td>
<td>0</td>
<td>&lt; 0.1</td>
<td>&lt; 0.1</td>
</tr>
</tbody>
</table>

All subjects who received ≥1 dose of investigational product. Treatment groups are based on the original randomized treatments received in FREEDOM. AEs coded using MedDRA v13.0. Cumulative osteonecrosis of the jaw cases: 6 cross-over, 7 long-term. Cumulative atypical femoral fracture cases: 1 cross-over, 1 long-term. Bone Hill et al. Lancet Diabetes Endocrinol 2017;5:513-23

Case

- 70 year old woman was diagnosed with osteoporosis
- 1 year earlier, she had experienced a Colles fracture when she fell while hiking
- BMD T-score: lumbar spine -2.0; total hip -3.0; femoral neck -2.8
- Began alendronate weekly which she tolerated well and took regularly
- After 5 years of therapy, she had not experienced additional fractures.
- Repeat BMD T-scores: lumbar spine -1.5; total hip -2.6; femoral neck -2.5
- Adherence is good, no secondary causes identified

OPTIONS
- “bisphosphonate holiday”
- continue alendronate
- switch to zoledronic acid
- switch to denosumab
- switch to teriparatide

Bisphosphonate “Drug Holiday”

- Justification
  - Protection from fragility fracture persists 1-2 years upon stopping therapy
  - Risk of atypical fracture may decrease when treatment stopped

- After 3-5 years of therapy:
  - Patients at moderate fracture risk: consider a “holiday”
  - Patients at high risk (low BMD, prior vertebral fracture, elderly): continue to treat and follow for 10 years


NOTE: No justification for drug holiday with any other osteoporosis drug
Bisphosphonate “Drug Holiday”

- An “opportunity” – not a necessity and not mandatory
- There is no “rule” that therapy must be stopped after any interval of time

That decision has to be made on a case-by-case basis

In my opinion, she would not be a candidate for a ‘Bisphosphonate Holiday’
Switching From Bisphosphonates to Denosumab

Patients who had previously been treated with bisphosphonates randomly assigned to a bisphosphonate or denosumab.

Data are least-squares means and 95% confidence intervals. p values, denosumab vs BP. * < 0.0001; ** < 0.01; *** < 0.01.


Relationship Between On-Treatment Total Hip BMD T-score and Non-vertebral Fracture Risk

Incidence of non-vertebral fracture at 1 year (%)

-3.0 -2.5 -2.0 -1.5 -1.0 -0.5

1.0 2.0 3.0 4.0 5.0 6.0

Total Hip T-score

Treating to a BMD target may now be feasible

Current non-vertebral fracture risk was strongly correlated with on target hip BMD

Osteoporosis: Long-term Treatment Plan

When concerned about hip fracture

-3-5 years

Low risk

High risk

Consider drug holiday

Continue therapy?

Denosumab

Diagrams and equations are not transcribed due to the limitations of the text-to-speech model.
Combining Osteoporosis Drugs

- There is no role for combining anti-remodeling agents
- Combining teriparatide with
  - bisphosphonates: no benefit on BMD
  - denosumab: faster, greater increases in BMD; no fracture data

Denosumab fully inhibits the increased resorptive response to teriparatide and substantially blunts the anabolic response.

New Anabolic Therapies: Phase 3 Study Designs

**ACTIVE - abaloparatide**

<table>
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<tr>
<th>Placebo</th>
<th>Abaloparatide</th>
<th>Alendronate</th>
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</thead>
<tbody>
<tr>
<td>18 Months</td>
<td>36 Months</td>
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**FRAME - romosozumab**

<table>
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<tr>
<th>Placebo</th>
<th>Denosumab</th>
<th>Romosozumab</th>
<th>Denosumab</th>
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</thead>
<tbody>
<tr>
<td>12 Months</td>
<td>24 Months</td>
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**ARCH - romosozumab**

<table>
<thead>
<tr>
<th>Alendronate</th>
<th>Alendronate</th>
<th>Romosozumab</th>
<th>Alendronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 Months</td>
<td>24 Months</td>
<td></td>
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Sclerostin Inhibitor: Romosozumab

**Phase 3: FRAME: Vertebral Fracture Risk Reduction**

**Year 1**

ClinicalTrials.gov identifier: NCT01575824

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Romosozumab</th>
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<tbody>
<tr>
<td>12% Fracture protection sustained during 12 months of denosumab therapy</td>
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</table>

**Year 2**

All patients on denosumab 60 mg Q6M

<table>
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<tr>
<th>Placebo</th>
<th>Romosozumab</th>
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<tbody>
<tr>
<td>24% Fracture protection sustained during 12 months of denosumab therapy</td>
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**ClinicalTrials.gov Identifier**: NCT01575824
Controversies in Osteoporosis

Summary

- Osteoporosis is a chronic, incurable medical problem deserving long-term management
- Even with bisphosphonates, the benefit:risks profile is favorable for at least 1–5 years in patients at high fracture risk
- A “bisphosphonate holiday” may be considered after 3–5 years for patients at low risk of fracture
- For continuing therapy after 3–5 years of bisphosphonates, switching to denosumab rather than continuing bisphosphonate should be considered
- If denosumab therapy is discontinued, switching to another anti-remodeling agent needs to be considered
- There is currently no role for the use of more than one osteoporosis drug at a time
Thank You

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