Long-term Osteoporosis Therapy
What To Do After 5 Years?

Developing a Long-term Management Plan

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Disclosures

I am disclosing financial relationships as follows:

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Michael McClung, MD 2017
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

Images Courtesy of Drs. David Dempster & Roger Zebazi

Osteoporosis Therapies

OBJECTIVES ¹,²

1. improve bone strength
2. reduce risk of fracture
3. prevent rapid bone loss (less commonly)

BENEFITS ²

1. effective protection from fractures
   - vertebral fracture by 60-70%
   - hip fracture by 40-50%
   - non-vertebral fracture by 20-35%
2. in general are well tolerated
3. in clinical trials, have a favorable safety profile

¹ Seeman E et al. Bone 2004;17 Suppl 2:23S-29S
Long-term Osteoporosis Therapy

Bisphosphonates and denosumab are the agents considered for long-term use

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

   Bone HG et al. Lancet Diabetes Endocrinol 2017;5:513-23
Vertebral Fractures with Zoledronic Acid

Years 1-3

- PBO: 10.9% (310/2853)
- ZOL: 70%† (62, 76)

Fracture protection persists with long term therapy

P = <0.001

Core study
Morphometric Vertebral Fractures

Years 4-6

- ZOL: 3.3% (92/2822)
- PBO: 3.0% (14/469)

Years 7-9

- ZOL: 4.4% (3/68)

Black DM et al. *J Bone Miner Res* 2012;27:243-54
Black DM et al. *J Bone Miner Res* 2015;30:934-44
Long-term Denosumab Therapy

Vertebral and Non-vertebral Fractures

Persistent reduction in fracture risk

Bone HG et al. Lancet Diabetes Endocrinol 2017; 5:513-23
Risks and Concerns with Long-term Therapy

*Bisphosphonates*

- Hypocalcemia
- Intolerance
  - upper GI symptoms: *oral drugs*
  - acute phase reaction: *IV drugs*
  - bone and muscle pain
- Inflammatory eye problems
- Atrial fibrillation
- Esophageal cancer: *oral drugs*
- Osteonecrosis of the jaw
- Atypical fractures
  - 1/1000 patients after 8-10 years

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**No increase with long-term therapy**

**Unproven relationship; minimal evidence of increased risk with long-term therapy**

**Concern here of risk of long-term therapy**
Atypical Femoral Fracture and Long-term Bisphosphonate Therapy

- 11,466 patients with femoral fracture
- 7430 typical hip fracture
- 142 atypical stress-type fractures
  - 10% occurs in untreated patients

Duration-dependent risk of AFF:
- 1.78/100,000 patient-years in first 2 yr
- 113/100,000 patient-years in years 8-9.9

Rapid decrease in risk when treatment is stopped

R Dell: personal communication

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**

<table>
<thead>
<tr>
<th>Exposure-adjusted Subject Incidence of Adverse Events (Rates per 100 Subject-years)</th>
<th>FREEDOM Years 1–3</th>
<th>Extension Years 1–7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong> (N = 3883)</td>
<td><strong>Cross-over Denosumab</strong> (N = 2206)</td>
<td><strong>Long-term Denosumab</strong> (N = 2343)</td>
</tr>
<tr>
<td>All AEs</td>
<td>156.1</td>
<td>96.8</td>
</tr>
<tr>
<td>Infections</td>
<td>30.7</td>
<td>20.7</td>
</tr>
<tr>
<td>Malignancies</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Eczema</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>&lt; 0.1</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>&lt; 0.1</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>10.4</td>
<td>10.1</td>
</tr>
<tr>
<td>Infections</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Cellulitis or erysipelas</td>
<td>&lt; 0.1</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Fatal AEs</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw</td>
<td>0</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Atypical femoral fracture</td>
<td>0</td>
<td>&lt; 0.1</td>
</tr>
</tbody>
</table>

N = number of 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 HG et al. *Lancet Diabetes Endocrinol* 2017;5:513-23
Osteoporosis Therapies

Fracture protection

- begins within months of starting therapy
- persists with long-term therapy
- wanes when treatment is stopped
  - even with bisphosphonates
Vertebral Fractures with Zoledronic Acid

Absolute risk of new vertebral fracture if therapy is stopped = 1%/year

No difference in incidence of non-vertebral fractures

Clinical Vertebral Fractures in FLEX Study

Cumulative Incidence of Fractures (%)

- ALN 5 years → Placebo 5 years: 5.4%
- Alendronate 10 years: 2.5%

Relative Risk (RR) ↓ 55%
P = 0.013

Black DM et al. JAMA. 2006;296:2927-38
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 to 10 years

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
Denosumab Drug Holiday?

Osteoporos Int (2016) 27:1677–1682
DOI 10.1007/s00198-016-3553-3

EDITORIAL

Cancel the denosumab holiday

M. R. McClung

OOC
Discontinuing Denosumab: BMD
Phase 2 Study in Women With Low BMD

Adapted from Miller PD, McClung M et al. Bone 2008;43:222-29
Discontinuing Denosumab After 8 Years

*Lumbar Spine BMD*

**Parent Study**

- Placebo
- Denosumab 210 mg Q6M
- Off-treatment

**Extension Study**

*All on DMAb Treatment*

**Observation**

- N = 52
- 16.8%
- N = 10
- 8.1%

**Study Month**

- 01 3 6 12 18 24 36 48 60 72 84 96 108

**Percentage Change From Baseline**

- 6.7%
- 5.1%

McClung M et al. ASBMR 2014
Discontinuing Denosumab: BMD

Phase 2 Study in Women With Low BMD

Phases 2 Study in Women With Low BMD

Discontinued Treatment

Placebo

210 mg Q6M

Open-label alendronate

 adaptation from Miller PD, McClung M et al. Adapted from Miller PD, McClung M et al. Bone 2008;43:222-29

*P < 0.001 at month 36 and = 0.05 at month 48 vs placebo.

†P = 0.008 at month 36 vs placebo.

Adapted from Miller PD, McClung M et al. Bone 2008;43:222-29

Serum CTx

BSAP

Median ng/mL (Q1, Q3)

0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6

0 6 12 18 24 30 36 42 48

Months

0 5 10 15 20 25

0 6 12 18 24 30 36 42 48

Months

OOC
Effect of Withdrawing Alendronate or E/P:

*Urinary NTx*

<table>
<thead>
<tr>
<th>Stratum 1 Only</th>
<th>Mean Percent Change (Mean Percent Change (± SE))</th>
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<tbody>
<tr>
<td></td>
<td>Mean Percent Change</td>
</tr>
<tr>
<td></td>
<td>-20</td>
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<tr>
<td></td>
<td>0</td>
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<tr>
<td></td>
<td>5</td>
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<td>6</td>
</tr>
</tbody>
</table>

OOC

Denosumab “Drug Holiday”?  

Vertebral Fractures After Discontinuing Denosumab Therapy

- At least 24 patients have been reported who experienced vertebral fractures within 3-18 months after discontinuing denosumab therapy. (1)
- Many or most have had multiple and/or severe fractures
- Raised concern about “rebound” risk of fracture
- Similar to rapid loss of fracture protection when estrogen therapy is discontinued (2,3)

1. Anastasilakis AD et al. J Bone Miner Res. 2017 Feb 27
2. Heiss G et al. JAMA 299:1036–45
Vertebral Fractures After Discontinuing Denosumab or Placebo in FREEDOM Study

- Vertebral fracture risk was assessed in patients who discontinued either placebo or denosumab in the FREEDOM study or who stopped denosumab in the FREEDOM Extension study and who had a follow-up at least 7 months after their last dose.

- Fracture risk increased upon stopping denosumab but not to levels greater than seen in those who stopped placebo.

Brown JP et al. ASBMR Abstract #1100, 2016
Effect of Withdrawing Hormone Therapy: 
*Hip Fracture in WHI*

- Within first year, of stopping hormone therapy, hip fracture rates approximate those in placebo group
- No evidence of rebound in fracture risk

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**Heiss G et al. JAMA. 2008;299:1036-45**
Effect of Withdrawing Hormone Therapy: 
Fractures in WHI

Heiss G et al. JAMA 2008;299:1036-45
Denosumab and Alendronate (DAPS Trial)
Cross-over Treatment after 12 Months

Switching from denosumab to alendronate, bone loss did not occurLea

Denosumab  Alendronate

Percent Change From Baseline

Lumbar spine

Total hip

Months

Freemantle N et al. Osteoporos Int 2012;23:317-26
Long-term Denosumab Therapy

Summary

• There are very few reasons to consider stopping denosumab therapy
  • intolerance or side effect
  • reaching a treatment “target”

• If therapy is stopped after a year or more, consider options to prevent rapid bone loss and fracture risk

• At present, the most appealing strategy would be to treat with a bisphosphonate for 2 years and to then re-evaluate the patient. (1)

Effects of Therapy on Total Hip BMD Through 10 Years

Total Hip BMD

0 1 2 3 4 5 6 7 8 9 10
Study Year

-2 -1 0 1 2 3 4 5 6 7 8 9 10
Percentage Change From Baseline

Denosumab

Alendronate 10 mg/d

Zoledronic acid 5 mg/y

9.2%
6.8%
4.6%

Study Year

1. Bone HG et al. Lancet Diabetes Endocrinol 2017 Published Online May 22, 2017
   http://dx.doi.org/10.1016/S2213-8587(17)30138-9
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 < 0.0001 denosumab vs BP.

The greater the increase in BMD, the greater reduction in NV fractures.

+1% BMD change = -11.11% in RR (95% CI -14.54% to -7.54%, p = 0)

*Bubble size ~ to # fractures in study*
Relationship Between On-Treatment Total Hip BMD T-score and Non-vertebral Fracture Risk

Treating to a BMD target may now be feasible

Current NV fracture risk was strongly correlated with on target hip BMD

Ferrari S et al. ASBMR; Seattle, WA; October 2015
Treat to Target: An Evolving Concept

Goal-Directed Treatment for Osteoporosis: A Progress Report From the ASBMR-NOF Working Group on Goal-Directed Treatment for Osteoporosis

Steven R Cummings,1 Felicia Cosman,2 E Michael Lewiecki,3 John T Schousboe,4 Douglas C Bauer,5 Dennis M Black,6 Thomas D Brown,7 Angela M Cheung,8 Kathleen Cody,9 Cyrus Cooper,10 Adolfo Diez-Perez,11 Richard Eastell,12 Peyman Hadji,13 Takayuki Hosoi,14 Suzanne Jan De Beur,15 Risa Kagan,16 Douglas P Kiel,17 Ian R Reid,18 Daniel H Solomon,19 and Susan Randall20

Cummings SR et al. J Bone Miner Res 2017;32:3-10
Osteoporosis: Long-term Treatment Plan

- **Raloxifene**
  - When concerned about hip fracture
  - After 12-24 months
  - 3-5 years

- **Bisphosphonate**
  - Low risk
  - High risk

- **Teriparatide/abaloparatide**
  - After 12-24 months
  - Continue therapy?

- **Denosumab**
  - Low risk
  - Consider drug holiday
  - High risk
  - Continue therapy?
  - Bisphosphonate for 1-2 years
  - If “target” is met

Re-treat
Osteoporosis Therapy:
Long-term Management Plan

- Decisions about starting therapy must be individualized
- After 3-5 years of bisphosphonates, consider
  - drug holiday for patients at modest risk
  - switching to denosumab if hip BMD still low
- Denosumab
  - very rarely a reason to stop therapy
  - if denosumab therapy is to be stopped, consider an alternative anti-resorptive (e.g. bisphosphonate) to prevent rapid bone loss

Photo courtesy of
Betsy Love McClung, RN, MN

McClung M. Personal opinion, 2017
Thank you

Working to prevent

Bone Attacks

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