Long-term Osteoporosis Therapy:  
*What to Do After 5 Years?*

Endocrine Fellows Foundation  
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Disclosures

I am disclosing financial relationships as follows:

Scientific Advisory Boards: Amgen, Radius

Honorarium for speaking: Amgen, Radius

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

Objectives

• To review
  • the benefits and risks of long-term therapy
  • effects of discontinuing bisphosphonate and non-bisphosphonate therapies
• To consider a strategy for long-term management of patients with osteoporosis
Case

- Healthy woman; menopause at age 52
  - Age 60: wrist fracture
  - Age 67: humerus fracture. BMD T-score -2.6 in lumbar spine and -2.9 at total hip. Begun on alendronate; well tolerated
  - Age 72: BMD T-score -1.8 in lumbar spine and -2.6 at total hip.

- Management choices:
  - discontinue alendronate therapy
  - continue alendronate therapy
  - switch to IV zoledronic acid
  - switch to denosumab
  - other
Osteoporosis Therapies

OBJECTIVES

1. improve bone strength
2. reduce risk of fracture

BENEFITS

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

Osteoporosis Therapies

1. Fracture protection
   - begins within months of starting therapy
   - continues with long-term therapy
   - wanes when treatment is stopped
Zoledronic Acid and Denosumab

Incidence of Vertebral Fracture

Vertebral fracture protection happens within first year of treatment

HORIZON Study ¹

FREEDOM Study ²

Zoledronic Acid and Denosumab
Cumulative Incidence of Hip Fracture

**Cumulative incidence of hip fracture**

**HORIZON Study**
- Hazard ratio, 0.59 (95% CI, 0.42–0.83)
- P=0.002

**FREEDOM Study**

Osteoporosis Therapies

1. Fracture protection
   - begins within months of starting therapy
   - persists with long-term therapy
   - wanes when treatment is stopped
Vertebral Fractures with Zoledronic Acid

Fracture protection persists with long term therapy

Years 1-3

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

P = <0.001

Years 4-6

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

Core study

Extension study

Morphometric Vertebral Fractures

Effects of Denosumab Treatment on Vertebral and Non-vertebral Fracture Risk

Vertebral fracture

Non-vertebral fracture

Effects of Therapy on Total Hip BMD Through 10 Years

**Total Hip BMD**

- **FREEDOM**
- **Extension**
- **Long-term Denosumab**
  - 9.2%
- **Alendronate 10 mg/d**
  - 6.8%
- **Zoledronic acid 5 mg/y**
  - 4.6%

**Percentage Change From Baseline**

**Study Year**

[Graph showing percentage changes over 10 years for different therapies.]

1. Bone HG et al. ASBMR; Seattle, WA; October 12, 2015; #LB-1157
Patients who had previously been treated with bisphosphonates randomly assigned to a bisphosphonate or denosumab.

Switching From Bisphosphonates to Denosumab

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

FNIH Meta-regression
Change in Total Hip BMD vs Reduction in Hip Fracture

Bubble size ~ to n fractures in study

Courtesy of Dr D Black et al, ASBMR 2015
Relationship Between On-Treatment Total Hip BMD T-score and Non-vertebral Fracture Risk

Treating to a BMD target may now be feasible
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
Osteoporosis Therapies

1. Fracture protection
   - begins within months of starting therapy
   - persists with long-term therapy
   - wanes when treatment is stopped
     - even with bisphosphonates
Osteoporosis Therapies: Safety 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% occur 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

May be a decrease in risk if treatment is stopped
R Dell: personal communication

In untreated patients: 0.3/100,000 patient-years

Dell RM et al. J Bone Miner Res. 2012;27:2544-50
## Denosumab: Long-term Safety

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

<table>
<thead>
<tr>
<th></th>
<th>FREEDOM Years 1–3</th>
<th>Extension Years 1–7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 3883)</td>
<td>Cross-over Denosumab (N = 2206)</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
Case

- Healthy woman; menopause at age 52
  - Age 60: wrist fracture
  - Age 67: humerus fracture. BMD T-score -2.6 in lumbar spine and -2.9 at total hip. Begun on alendronate; well tolerated
  - Age 72: BMD T-score -1.8 in lumbar spine and -2.6 at total hip.

- Management choices:
  - discontinue alendronate therapy
  - continue alendronate therapy
  - switch to IV zoledronic acid
  - switch to denosumab
  - other
Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research


Post-menopausal women treated with oral (≥ 5yrs) 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 (5)
Bisphosphonate “Drug Holiday”

- An “opportunity” – not a necessity
  - 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


**NOTE:**

No evidence that a “drug holiday” reduces risk of any complication of therapy
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: BMD
Phase 2 Study in Women With Low BMD

**Serum CTx**

<table>
<thead>
<tr>
<th>Months</th>
<th>Median ng/mL (Q1, Q3)</th>
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<tr>
<td>0</td>
<td>1.2</td>
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<tr>
<td>6</td>
<td>1.2</td>
</tr>
<tr>
<td>12</td>
<td>1.4</td>
</tr>
<tr>
<td>18</td>
<td>1.4</td>
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<td>24</td>
<td>1.6</td>
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<td>36</td>
<td>1.6</td>
</tr>
<tr>
<td>42</td>
<td>1.6</td>
</tr>
<tr>
<td>48</td>
<td>2.0</td>
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</table>

**BSAP**

<table>
<thead>
<tr>
<th>Months</th>
<th>Median mcg/L (Q1, Q3)</th>
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<tbody>
<tr>
<td>0</td>
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<td>6</td>
<td>20</td>
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<tr>
<td>12</td>
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<td>30</td>
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<tr>
<td>36</td>
<td>25</td>
</tr>
<tr>
<td>42</td>
<td>25</td>
</tr>
<tr>
<td>48</td>
<td>25</td>
</tr>
</tbody>
</table>

Discontinued Treatment

Placebo

210 mg Q6M

Open-label alendronate

*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
Discontinuing Denosumab After 8 Years
Lumbar Spine BMD

**Parent Study**
- Placebo
- Denosumab 210 mg Q6M
- Off-treatment

**Extension Study**
- All on DMAb Treatment

**Observation**

<table>
<thead>
<tr>
<th>Study Month</th>
<th>Percentage Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 3 6 12 18 24 36</td>
<td>-7 -6.7% -6.7%</td>
</tr>
<tr>
<td>48</td>
<td>16.8%</td>
</tr>
<tr>
<td>60</td>
<td>8.1%</td>
</tr>
<tr>
<td>72</td>
<td></td>
</tr>
<tr>
<td>84</td>
<td></td>
</tr>
<tr>
<td>96</td>
<td>N = 52</td>
</tr>
<tr>
<td>108</td>
<td>N = 10</td>
</tr>
</tbody>
</table>

McClung M et al. *Osteoporos Int.* 2017;28:1723-32
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
Fracture Risk after Stopping Denosumab

- Subgroup of 797 subjects (470 placebo, 327 denosumab), who discontinued study drug in FREEDOM after 2-5 doses.

- During the off-treatment period (median 0.8 years per subject), 42% versus 28% of placebo- and denosumab-treated subjects, respectively, initiated other therapy.

Following discontinuation, similar percentages of subjects in both groups sustained a new fracture (9% placebo, 7% denosumab)

Fracture rate per 100 subject-years of 13.5 for placebo and 9.7 for denosumab

Hazard ratio [HR] 0.82; 95% confidence interval [CI], 0.49–1.38, adjusted for age and total hip BMD T-score at baseline.

There was no apparent difference in fracture occurrence pattern between the groups during the off-treatment period.

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
Fracture Risk after Stopping Denosumab

• Protection from vertebral fractures is quickly lost upon stopping denosumab

_BUT_

• There is no apparent excess or rebound in vertebral fracture risk upon stopping therapy

McClung M. Personal opinion, 2017
Discontinuing Denosumab

*Other Information*

- Bone loss and rise in serum CTX is attenuated in patients who stop denosumab but who took bisphosphonates before denosumab therapy.
  
  Ferrari S et al. ECTS 2016

- Bone loss after stopping denosumab is attenuated in patients who then receive anti-remodeling agents

  McClung M et al. *Osteoporos Int.* 2017;28:1723-32
Denosumab and Alendronate (DAPS Trial)
Cross-over Treatment after 12 Months

Switching from denosumab to alendronate, bone loss did not occur

Percent Change From Baseline

 Months

Denosumab
Alendronate

Lumbar spine
Total hip

Freemantle N et al. Osteoporos Int. 2012;23:317-26
Discontinuing Denosumab

Change in Prescribing Information

- A new caution has been added to Prolia label:
  - *Multiple vertebral fractures have been reported following Prolia discontinuation.*
  - *Consider transitioning to another antiresorptive agent if therapy is discontinued.*
Discontinuing Denosumab

Change in Prescribing Information

- A new caution has been added to Prolia label:
  - Multiple vertebral fractures have been reported following Prolia discontinuation.
  - Consider transitioning to another antiresorptive agent if Prolia is discontinued.
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 1-2 years, re-evaluating the patient at regular intervals

McClung MR. Cancel the denosumab holiday. Osteoporos Int. 2016;27:1677-82
Osteoporosis Therapy After 5 Years

Summary

- **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
Case: Management

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  - Age 60: wrist fracture
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  - Age 72: BMD T-score -1.8 in lumbar spine and -2.6 at total hip.

- Management choices:
  - Discontinue alendronate therapy
  - Continue alendronate therapy
  - Switch to IV zoledronic acid
  - Switch to denosumab
  - Other
Osteoporosis: Long-term Treatment Plan

- **Raloxifene**
  - When concerned about hip fracture
  - After 18-24 months

- **Bisphosphonate**
  - 3-5 years
  - After 18-24 months

- **Teriparatide**
  - After 18-24 months

- **Denosumab**
  - If “target” is met

- **Denosumab**
  - Low risk
  - High risk

- **Bisphosphonate**
  - 1 dose ZOL
  - 2 years ALN

Re-treat
Consider drug holiday
Thank you

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