Sequencing Osteoporosis Therapies

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Osteoporosis is a chronic, incurable condition requiring prolonged management

- On-treatment hip BMD correlates with current fracture risk

- Skeletal benefits of all osteoporosis therapies wane upon discontinuation of treatment
  - *It is important to develop a strategy for long-term treatment*

- Currently available osteoporosis drugs have
  - different mechanisms of action
  - different contraindications
  - different potency or effectiveness
  - different contraindications

- The sequence with which drugs are given may have important clinical ramifications
Osteoporosis Treatment Options - 2022

- **Anti-remodeling agents** (*inhibit bone turnover*)
  - Estrogen (approved for prevention only)
  - Estrogen agonists/antagonist (raloxifene)
  - Bisphosphonates (oral and IV)
  - RANK ligand inhibitor (denosumab)

- **Osteoanabolic agents** (*activate bone formation*)
  - Remodeling stimulators (*increase formation and resorption*)
    - Parathyroid hormone receptor activators
      - teriparatide and abaloparatide
    - Modeling stimulator (*increase formation, decrease resorption*)
      - Sclerostin inhibitor
      - romosozumab
Switching Osteoporosis Therapies:  
*When to Consider Switching*

A. Inadequate response to an anti-remodeling agent

B. After 5 years of bisphosphonate therapy

C. When stopping a non-bisphosphonate anti-remodeling drug (denosumab, estrogen, raloxifene)

D. At the end of a course of osteoanabolic therapy
Switching Osteoporosis Therapies:  
A. Inadequate Response to an Anti-remodeling Drug

Healthy 80 year-old man with osteoporosis was begun on alendronate 70 mg weekly

After 2 years, BMD values had not changed

<table>
<thead>
<tr>
<th>T-scores at</th>
<th>Baseline</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumber spine</td>
<td>-2.6</td>
<td>-2.7</td>
</tr>
<tr>
<td>Total hip</td>
<td>-2.2</td>
<td>-2.2</td>
</tr>
</tbody>
</table>

Management:
- Assess compliance with dosing regimen
- Look again for secondary causes
- Consider poor absorption (measure serum CTX)
- Consider switching therapies – perhaps to a parental drug
Switching Osteoporosis Therapies:  
*PO Alendronate to IV Zoledronate*

Patients on alendronate randomly assigned to continue therapy or to receive zoledronate 5 mg IV

Better results could be expected in patients who were poorly compliant with oral alendronate or who had poor absorption of oral drugs.
Switching Osteoporosis Therapies: Bisphosphonates to Denosumab

Patients who had previously been treated with alendronate randomly assigned to continue alendronate or switch to denosumab

Kendler DL et al. *J Bone Miner Res* 2010;25:72-81
Switching Osteoporosis Therapies:

*Switching from Oral Bisphosphonate*

- Switching therapy is appropriate when a patient is intolerant to therapy, has difficulty with the dosing regimen or has an inadequate BMD response.

- The choice (IV bisphosphonate, denosumab or osteoanabolic agent) will depend on the usual determinants – current BMD and fracture risk, other medical issues, patient preference and cost.

- In general, the response to any therapy when given after alendronate is smaller than when given to a treatment-naïve patient.

McClung MR. *Curr Osteoporos Rep* 2017;15:343-52
Healthy 80 year-old woman with osteoporosis was begun on alendronate 70 mg weekly

2 years later, he experienced 2 vertebral fractures

T-scores now:

- Lumber spine -3.0; Total hip -2.2

**Management:**
- Assess compliance with dosing regimen
- Look again for secondary causes
- Consider poor absorption (measure serum CTX)
- Consider switching therapies – perhaps to an osteoanabolic agent

*This patient now meets criteria for being at very high fracture risk*
AACE and IOF suggest categorizing patients at low, high or very high risk of fracture.
Choice of Treatment According to Level of Risk

Osteoanabolic therapies are recommended for patients at very high fracture risk

Very high risk

abaloparatide, romosozumab, teriparatide
alternatives: denosumab, zoledronate

Consider anabolic agent followed by inhibitor of bone resorption

2. Kanis JA et al. Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures. Osteoporus Int 2020;31:1-12
Switching Osteoporosis Therapies: 
*Anti-remodeling Drug to an Osteoanabolic Agent*

- In treatment-naïve patients, BMD and fracture protection are better with an anabolic drug vs a bisphosphonate.
- The BMD response to anabolic agents is smaller in patients previously treated with an anti-resorptive drug.
- There are very limited fracture data with the sequence of an anti-remodeling drug followed by an anabolic agent.

Reasons to switch from an anti-remodeling drug to an osteoanabolic agent:
- inadequate response to an anti-remodeling agent
- marked increase in patient’s fracture risk
Switching Osteoporosis Therapies:
B. After 5 Years of Bisphosphonate Therapy

• After 5 years of bisphosphonate therapy
  • for patients who no longer meet treatment criteria, a “bisphosphonate holiday” is justified
  • for patients remaining at high risk of fracture –i.e., who still meet treatment criteria:
    • no additional increase in BMD or improved fracture risk reduction with longer term therapy
    • increasing risk of atypical femoral fracture

Camacho PM et al. Endocr Pract 2020;26:564-70
Dennison EM et al. Osteopros Int 2019;30:1733-43
Switching Osteoporosis Therapies: After 5 Years of Bisphosphonate Therapy

- BMD gain plateaus after 5 years of bisphosphonate therapy
- Risk of atypical femoral fracture (AFF) increases with long-term bisphosphonate therapy (~1/1000 after 8-10 years)
  - AFF risk decreases upon stopping therapy

This combined with relatively slow offset of fracture protection upon stopping a bisphosphonate is justification for “drug holiday” in patients at low fracture risk

Patients remaining at high risk on bisphosphonate need to continue therapy

There is no justification for continuing bisphosphonates for more than 5 years at a time
Switching Osteoporosis Therapies: 
*After 5 Years of Bisphosphonate Therapy*

Healthy 75 year-old woman with osteoporosis and prior history of humerus fracture was begun on alendronate 70 mg weekly.

After 2 years, BMD values had improved

<table>
<thead>
<tr>
<th>T-scores at</th>
<th>Baseline</th>
<th>24 months</th>
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</thead>
<tbody>
<tr>
<td>Lumber spine</td>
<td>-3.2</td>
<td>-2.7</td>
</tr>
<tr>
<td>Total hip</td>
<td>-2.7</td>
<td>-2.4</td>
</tr>
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• **Management:**
  • Not a candidate for bisphosphonate holiday
  • Continuing a bisphosphonate will not improve BMD or fracture risk and will be associated with increasing risk of atypical femoral fracture
  • Switching of denosumab or an osteoanabolic agent will improve BMD
Switching Osteoporosis Therapies: 
*Bisphosphonate to Denosumab*

- BMD gain plateaus after 5 years of bisphosphonate therapy but not with denosumab

**Transition from bisphosphonate to denosumab**

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

Bone HG et al. *Lancet Diabetes Endocrinol* 2017;5:513-23
Black DM et al. *J Bone Miner Res* 2015;30:934-44

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

Switching Osteoporosis Therapies:  
*Alendronate to Osteoanabolic Agent*

- In patients previously treated with alendronate, volumetric BMD and estimated hip strength increased significantly with romosozumab but not with teriparatide.
Switching Osteoporosis Therapies: 
*After 5 Years of Bisphosphonate Therapy*

- For patients remaining at high risk of fracture after 5 years of bisphosphonate therapy, there is no justification for continuing the bisphosphonate.

- Switching to either denosumab or an anabolic agent is recommended, the choice being driven by the patient’s current risk of fracture.

- It appears that the BMD response when switching to romosozumab is greater than occurs with a switch to teriparatide.

- However, we have no data about fracture risk with any of these transitions.
# Switching Osteoporosis Therapies: C. Upon Discontinuation of Estrogen or Denosumab

A 70-year-old woman began therapy for osteoporosis with denosumab. After 4 years of therapy, her BMD had substantially increased.

<table>
<thead>
<tr>
<th>T-scores at</th>
<th>Baseline</th>
<th>4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumber spine</td>
<td>-2.8</td>
<td>-2.0</td>
</tr>
<tr>
<td>Total hip</td>
<td>-2.4</td>
<td>-1.8</td>
</tr>
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- **Reasons to discontinue denosumab include**
  - the development of a drug-related adverse event
  - patient reaches an acceptable BMD or fracture risk target
  - (insurance coverage, cost, etc.)

- **Considerations:**
  - There is no limit to the duration of denosumab use
  - Despite increases in BMD, she still has osteoporosis
  - Discontinuing therapy will result in rapid loss of her BMD gain and loss of vertebral fracture protection

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Lewiecki EM, Binkley N, Bilezikian JP. *J Bone Miner Res* 2019;34:605-6
Miller PD, McClung M et al. *Bone* 2008;43:222-29
Cummings SR et al. *J Bone Miner Res* 2018;33:190-8
Switching Osteoporosis Therapies: Discontinuing Denosumab

Rapid loss of BMD to baseline due to rebound in bone remodeling

*Rapid loss of vertebral fracture protection*

Adapted from Miller PD, McClung M et al. *Bone* 2008;43:222-29
Cummings SR et al. *J Bone Miner Res* 2018;33:190-8
Switching Osteoporosis Therapies: 
Upon Discontinuation of Estrogen or Denosumab

- Discontinuing estrogen results rapid bone loss due to rebound in bone remodeling
- In WHI study, the fracture protection associated with estrogen therapy was quickly lost when estrogen was discontinued
- Transitioning to alendronate (but not raloxifene) preserves BMD

Heiss G et al. JAMA 2008;299:1036-45

Switching Osteoporosis Therapies: 
*Discontinuing Denosumab*

- Neither raloxifene nor risedronate prevents bone loss and remodeling rebound upon stopping denosumab.
- Bisphosphonates are effective after short-term therapy but less so after longer-term denosumab therapy.

2.4 ± 0.2 years \(\text{Zoledronate after denosumab}\) 4.6 ± 1.6 years
Switching Osteoporosis Therapies: Discontinuing Denosumab

- This study compared zoledronate administration at 6 or 9 months after discontinuation of denosumab or, in observational group, if serum CTX rose above premenopausal reference range or at 6 months
- In some patients, a second dose of zoledronate, given 3-6 months after the first dose, may be required

Sölling AS et al. Treatment with zoledronate subsequent to denosumab in osteoporosis: a randomized trial. J Bone Miner Res 2020;35:1858-70
Switching Osteoporosis Therapies: Discontinuing Denosumab

- After 2 or more years of denosumab therapy, all patients should receive either zoledronate or alendronate if therapy is discontinued
  - Close monitoring response with serum CTX and BMD is appropriate with addition of another dose of zoledronate if significant BMD loss or rise in CTX to above the premenopausal reference range is observed
    Tsourdi E et al. *Bone* 2017;105:11-7

- Anabolic agents after denosumab:
  - marked bone loss with teriparatide
  - preservation of BMD with romosozumab after 12 months of denosumab, no data after longer-term therapy

McClung Mr et al. *JBMR Plus* 2021;5:e10512
Switching Osteoporosis Therapies:

D. Upon Completion of Course of Osteoanabolic Therapy

72 year-old woman had a prior history of wrist and pelvic fractures and then recently sustained 3 vertebral fractures while gardening. She was begun on abaloparatide 80 ugm daily which she has taken for 18 months.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumber spine</td>
<td>-3.2</td>
<td>-2.7</td>
</tr>
<tr>
<td>Total hip</td>
<td>-2.6</td>
<td>-2.4</td>
</tr>
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Considerations:
- This patient meets recently defined criteria for “very high risk”
- Anabolic therapy is appropriate
- The duration of the bone-building effects of all anabolic agents is limited, and those effects wane with continued use
- Discontinuing therapy results in rapid loss of BMD

McClung MR. Aging Clin Exp Res. 2021;33:775-91
Osteoanabolic Therapy vs Bisphosphonates

VERO Study and ARCH Trial

Key Point: Teriparatide and romosozumab reduce fracture risk better than do oral bisphosphonates

VERO Study

<table>
<thead>
<tr>
<th>Month</th>
<th>Vertebral fracture</th>
<th>Clinical fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>12/574</td>
<td>6.3</td>
</tr>
<tr>
<td>24</td>
<td>20/516</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Hazard ratio 0.48
P=0.0009

Risk ratio 0.48
P=0.0009

ARCH Trial

Vertebral fracture

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Alendronate Romosozumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.3</td>
<td>4.0</td>
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</table>

Risk ratio 0.63
P=0.003

At 12 months
Non-vert fracture: RRR 26% p = 0.06
Clinical fracture: RRR 28% (95% CI 4.46)

First Nonvertebral Fracture in Time-to-Event Analysis

At study end, hip fracture risk reduced by 38%
BMD Upon Stopping Anabolic Therapy

Percentage change from baseline over time for lumbar spine and total hip BMD with Teriparatide and Placebo groups.

- **Lumbar Spine**
  - Teriparatide: 8.1% increase at Year 1, 3.7% decrease by Year 2
  - Placebo: No significant change

- **Total Hip**
  - Teriparatide: No significant change
  - Placebo: No significant change

McClung MR et al. J Bone Miner Res 2018;33:1397-1406
Osteoporosis Therapies

Bone Mineral Density – Lumbar Spine

**Key Point:** Anti-remodeling therapy after an anabolic agent results in stable or increased BMD.

Responses to denosumab appear to be greater than with alendronate.

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*Long-term anti-remodeling therapy*

- **DMAB**
- **ALN**

**Key Points:***

- **TPTD** = teriparatide; **ABALO** = abaloparatide; **ROMO** = romosozumab; **DMab** = denosumab; **ALN** = alendronate.
**Osteoanabolic Therapy**

*Bone Mineral Density – Total Hip*

**Key Points:** The BMD advantages of anabolic therapies persist or improve upon transitioning to an anti-remodeling agents

Responses to denosumab appear to be greater than with alendronate

![Graph showing mean percentage change from baseline over months for different treatments: TPTD, ABALO, ROMO, ALN, and DMab.](image)

- **TPTD** = teriparatide
- **ABALO** = abaloparatide
- **ROMO** = romosozumab
- **ALN** = alendronate
- **DMab** = denosumab
Key Point: The fracture protection afforded by 12-18 months of anabolic therapy persists for at least 2 years after transitioning to an anti-remodeling agent.

PBO = placebo; ABALO = abaloparatide; ROMO = romosozumab; DMab = denosumab; RRR = relative risk reduction.
Switching Osteoporosis Therapies: 
Osteoanabolic to Anti-remodeling Drug

- Switching to either a bisphosphonate or denosumab should follow any course of osteoanabolic therapy to maintain or improve bone density and to maintain fracture protection.

- The choice of follow-on therapy is driven by the patient’s current fracture risk and BMD, especially at the hip.

- After an anabolic agent, the BMD response to denosumab appears to be greater than with alendronate.
Switching Osteoporosis Therapies:

Summary

Reasons to switch drugs:

• Inadequate response to an anti-remodeling agent – parenteral drug
• After 5 years of bisphosphonate therapy – denosumab or anabolic
• When stopping a non-bisphosphonate anti-remodeling drug (denosumab, estrogen, raloxifene) – usually a potent bisphosphonate
• At the end of a course of osteoanabolic therapy – bisphosphonate or denosumab
• The choice of the next agent will depend upon the initial drug, the patient’s response to that treatment and the patient’s current status and fracture risk
Switching Osteoporosis Therapies:
Summary

- Osteoporosis requires life-long management
- Optimal management must be individualized but will involve sequential use of different classes of osteoporosis drugs

- Note that the final drug an any sequence of therapies will likely be zoledronate
Thank you

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Request slides at
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Q&A

Dr Mike McClung
On behalf of IOF, we thank you for your participation in this webinar