Treatments for Osteoporosis: Expected Benefits, Potential Harms, and Drug Holidays

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May 2014
Learning Objectives

- Overview of osteoporosis management
- Outline efficacy and risks of bisphosphonates
- Discuss indications for drug holiday and how to monitor patients during that time
Bisphosphonates for treatment of osteoporosis

Expected benefits, potential harms, and drug holidays

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Canadian Family Physician • Le Médecin de famille canadien | VOL 60: APRIL • AVRIL 2014
Bone Strength

Biomechanical, biological and genetic factors

Bone Quality + Bone Density + Bone Geometry

Bone mineral content
Bone turnover
Activation Frequency
Damage accumulation
Quality of collagen

Bone diameter
Cortical thickness

Adapted from R.Rizzoli 2005
Fracture Risk Assessment: Importance of Using Tools
# Fracture Risk Assessment tools

<table>
<thead>
<tr>
<th>CAROC*</th>
<th>FRAX(^{†})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk Factors:</strong></td>
<td><strong>Additional Risk Factors:</strong></td>
</tr>
<tr>
<td>ᵃ Sex</td>
<td>ᵃ Low BMI</td>
</tr>
<tr>
<td>ᵃ Age</td>
<td>ᵃ Parental history of fracture (especially hip)</td>
</tr>
<tr>
<td>ᵃ BMD</td>
<td>ᵃ Current smoking</td>
</tr>
<tr>
<td>ᵃ Fragility fracture after 40</td>
<td>ᵃ Alcohol intake (\geq 3) units/day</td>
</tr>
<tr>
<td>ᵃ Systemic glucocorticoid use ((\geq 3) months)(^{†})</td>
<td>ᵃ Rheumatoid arthritis, or other secondary causes of osteoporosis</td>
</tr>
</tbody>
</table>

Calibrated with Canadian data and validated in Canadians

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*Canadian Association of Radiologists and Osteoporosis Canada, 2010

\(^{†}\) \(\geq 3\) months in the prior year of a prednisone equivalent dose \(\geq 7.5\)mg daily

\(^{‡}\) Fracture Risk Assessment Tool of the World Health Organization

Fracture Risk Assessment

CAROC Assessment Tool Stratification

Individuals with a T-score for the lumbar spine or total hip ≤ −2.5 should be considered to have at least moderate risk.

* At least three months cumulative use during the preceding year at a prednisone-equivalent dose ≥ 7.5 mg daily

How do we Choose Pharmacological therapy?

<table>
<thead>
<tr>
<th>Type of Fracture</th>
<th>Antiresorptive Therapy</th>
<th>Bone Formation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hip</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Non-Vertebral*</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

+ In clinical trials, non-vertebral fractures are a composite endpoint including hip, femur, pelvis, tibia, humerus, radius, and clavicle.

* For postmenopausal women, ✓ indicates first line therapies and Grade A recommendation. For men requiring treatment, alendronate, risedronate, and zoledronic acid can be used as first line therapies for prevention of fractures [Grade D].

** Estrogen or hormone therapy can be used as first line therapy in women with menopausal symptoms.
Bisphosphonates

- Anti-Fracture efficacy and cost-effectiveness documented

- 1st line agents for treatment of patients at high risk for fragility fracture

Bisphosphonates

- Inhibit osteoclastic activity and reduce bone remodeling -> increase BMD, lower fracture risk
- Prolonged residence in the skeleton
- Concerns have been raised:
  - Over-suppression of bone turnover
  - Microdamage accumulation and microcrack progression
  - Over-mineralization and greater homogeneity of crystalline maturity
  - Advanced glycation end-products loaded collagen

Ettinger B et al. 2013 Bone epub Feb 2013
Bisphosphonates: good *and* bad?

- Osteonecrosis of the jaw
- Atypical femur fractures
- Atrial fibrillation
- Kidney injury
- Oesophageal cancer
Osteonecrosis of the Jaw

- Presence of exposed bone in the maxillofacial region that does not heal within 8 weeks of
- In the absence of radiation therapy
- Incidence between 1 in 10,000 to 1 in 100,000 patient-treatment-years.
- Higher in oncology population
- Recommendations for elective or urgent dental procedures:
Atypical Femur Fractures

- Case reports
- Case series
- RCT re-analyses
- Cohort studies
- Case-control studies
- Meta-Analysis

Insufficiency fracture
Associated with bisphosphonate use

Feldstein A et al. *J Bone Miner Res.* 2012; 27: 977-86
Shane E et al *J Bone Miner Res.* Epub 2013 May 28
Incidence of AFF

- Incidence estimated to be
  - 1.78/100,000 p-years with exposure of < 2 years
  - 113/100,000 p-years with exposure 8 to 10 years
- Meta-analysis shows increased risk of subtrochanteric, diaphyseal and atypical fractures with bisphosphonate use

¹Dell RM et al. J Bone Miner Res 2012; 27: 2544-50
Atypical Femur Fractures

ASBMR Task Force 2013 Revised Case Definition of AFFs

- Associated with minimal or no trauma
- Transverse and originates at the lateral cortex (may become oblique as progresses across femur)
- Complete fractures extend through both cortices and may be associated with a medial spike;
- Incomplete fractures involve only the lateral cortex
- Noncomminuted or minimally comminuted
- Localized periosteal reaction of the lateral cortex present at fracture site ("beaking" or "flaring")

(Shane et al. J Bone Miner Res. 2014;29:1-24)

Additional features which may be present but are not required:
- Generalized increase in cortical thickness
- Unilateral or bilateral prodomal pain in the groin or thigh
- Bilateral incomplete or complete femoral diaphysis fractures
- Delayed healing

Specifically excluded are:
- Fractures of the femoral neck
- Intertrochanteric fractures with spiral subtrochanteric extension
- Periprosthetic fractures
- Pathological fractures associated with primary or metastatic bone tumors and miscellaneous bone diseases (eg, Paget’s disease, fibrous dysplasia)
Long-term Adverse Events associated with Bisphosphonate Use

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Incidence</th>
<th>Risk Factors</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteonecrosis of the Jaw</td>
<td>&lt;1/100,000 person-years</td>
<td>Poor oral hygiene, diabetes, glucocorticoid use and chemotherapy</td>
<td>Hold bisphosphonates 3 months prior to intervention and resume once healing is documented by dentist</td>
</tr>
<tr>
<td>Atypical Femur Fractures</td>
<td>2 à 110 / 100,000 person-years</td>
<td>Cumulative duration of bisphosphonates use (&gt;5 years), use of glucocorticoids, proton pump inhibitors</td>
<td>Use bisphosphonates ONLY in patients at moderate or high risk of fractures. Consider drug holiday. Inquire about pain in groin or thigh.</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>Lack of data to establish link</td>
<td>Barrett’s esophagus, severe GERD</td>
<td>Avoid oral bisphosphonates in patients with risk factors.</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>After revision from FDA, there is not enough evidence to support association</td>
<td>-</td>
<td>No need to consider this potential adverse event when prescribing anti-osteoporosis medication.</td>
</tr>
</tbody>
</table>

Figure 1. Risks of major osteoporotic fracture and other rare events

- Bis-ONJ*: 1.03
- Bis-AFF (8 y)': 78
- Bis-AFF (2 y)': 2
- Death by murder': 1.62
- Fatal MVA$: 8.4

Major osteoporotic fracture in low-risk women**: 650
Major osteoporotic fracture in moderate-risk women**: 1600
Major osteoporotic fracture in high-risk women**: 3100

INCIDENCE PER 100,000 PERSON-YEARS
How long should we keep patients on therapy?

- Usually limited to bisphosphonate therapy
- Concerns arise because:
  - Prolonged residence of bisphosphonates in bone
  - Over-suppression of bone remodeling
- Patient’s risk for fracture
- Affinity of bisphosphonate for bone
Concept of Drug Holiday

- Alendronate data
- Risedronate
- Zoledronic Acid data
- NO data on drug holiday with raloxifene or denosumab but, we know that if you stop these medications, there is no residual effect of therapy on bone remodeling
Duration of Bisphosphonate Therapy and Drug Holiday

<table>
<thead>
<tr>
<th>Fracture Risk</th>
<th>Duration of therapy</th>
<th>Duration of Drug holiday</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;10%)</td>
<td>No indication for bisphosphonates</td>
<td></td>
</tr>
<tr>
<td>Moderate (10-20%)</td>
<td>Between 5 and 7 years</td>
<td>1 to 3 years depending on the bisphosphonate used (risedronate &lt; alendronate &lt; zoledronic acid)</td>
</tr>
<tr>
<td>Elevé (&gt; 20%)</td>
<td>Do not stop therapy or change to another class of agents</td>
<td>Monitor for adverse events</td>
</tr>
</tbody>
</table>

What do we Monitor during a Drug Holiday?
-Treat to Target-

- Monitor Fracture Risk
- Inquire about Fractures
- Bone Turnover Markers
- Bone Mineral Density
FRAX- Treatment Target?

**Table:** Risk of incident fractures according to change in FRAX scores between DXA scans (Cox analysis).

<table>
<thead>
<tr>
<th></th>
<th>All women (N=11,049)</th>
<th>Untreated (N=4,515)</th>
<th>Treated MPR ≥0.80 (N=2,621)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95%CI)</td>
<td>p</td>
<td>Hazard Ratio (95%CI)</td>
</tr>
<tr>
<td>1st quartile (smallest change)</td>
<td>1.05 (0.81:1.35)</td>
<td>0.763</td>
<td>1.52 (0.89:2.60)</td>
</tr>
<tr>
<td>2nd quartile</td>
<td>1.00 (0.78:1.29)</td>
<td>0.921</td>
<td>1.13 (0.73:1.75)</td>
</tr>
<tr>
<td>3rd quartile</td>
<td>0.97 (0.76:1.23)</td>
<td>0.684</td>
<td>0.76 (0.49:1.17)</td>
</tr>
<tr>
<td>4th quartile (largest change)</td>
<td>1 ref</td>
<td>1</td>
<td>1 ref</td>
</tr>
<tr>
<td>linear trend across quartiles</td>
<td>0.806</td>
<td>0.298</td>
<td>0.84</td>
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Risk of incident major fractures according to change in FRAX scores

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</tr>
<tr>
<td>1st quartile (smallest change)</td>
<td>1.14 (0.69:1.91)</td>
<td>0.205</td>
<td>0.97 (0.31:3.04)</td>
</tr>
<tr>
<td>2nd quartile</td>
<td>0.84 (0.41:1.71)</td>
<td>0.360</td>
<td>1.40 (0.42:4.63)</td>
</tr>
<tr>
<td>3rd quartile</td>
<td>1.17 (0.71:1.93)</td>
<td>0.560</td>
<td>1.68 (0.72:3.92)</td>
</tr>
<tr>
<td>4th quartile (largest change)</td>
<td>1 ref</td>
<td>1</td>
<td>1 ref</td>
</tr>
<tr>
<td>linear trend across quartiles</td>
<td>0.271</td>
<td>0.567</td>
<td>0.366</td>
</tr>
</tbody>
</table>

Leslie WD, Majumdar SR, Morin SN et al ASBMR 2013, Baltimore, MD
What are the Therapeutic Options After a Drug Holiday

Remember to assess the risk for fractures with CAROC or FRAX

Always consider patient’s preference

- Resume bisphosphonate
- Change class: Denosumab
- Consider to change over to anabolic agent (teriparatide) but, restriction of reimbursement by Provincial Drug Plan
Key Messages

- Use fracture assessment tools
- Avoid basing your treatment decisions on BMD alone
- Use anti-osteoporosis medications only in patients at moderate and high risk for fractures
- Monitor adherence, tolerability, fractures, BMD and bone turnover markers
- Consider a drug holiday in patients at low and moderate risk after 5 to 7 years of treatment with bisphosphonates
Questions?

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