Bisphosphonate Drug Holiday: Who, When and How Long?

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Family Medicine Forum 2014 Québec
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Disclosures

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• Research grant: Amgen, Merck
• Consultant to: Amgen, Eli Lilly

Dr Beaulieu:
• Consultant to Amgen
Learning Objectives

• Discuss fracture risk assessment and treatment options for patients at high risk for fractures

• Describe adverse clinical events that have been associated with long term use of bisphosphonates

• Review the evidence to support a strategy towards optimal duration of therapy and drug holiday for patients on bisphosphonates
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
FP’s role

• As Family Physician: important role to play for identification, investigation and treatment initiation in patients who would benefit from anti-osteoporosis treatment

• Ensure adherence and compliance in our patients

• Evaluate, monitor and stop treatment if indicated
FP’s role

• Treatment indication changes: primary prevention in the 1990... guidelines of 2002 and 2010... fracture risk... drug holiday in 2014...

• Keep it simple!

• No absolute truth or recommendation about drug holiday but ...

• Prevent fracture but cause no harm
Mrs. Roy

• 66 y.o., has been on risedronate 35 mg once a week and vitamin D 1000 IU daily for the last 7 years after wrist fracture at age 59

• Initial BMD
  – Lumbar spine T score -2.8
  – Femoral Neck T score -2.5
  – CAROC 10 year absolute risk at the time was high

• High BP for which she takes HCTZ, no smoking, no alcohol, no family history of fractures
Mrs. Roy

• Tolerates treatment well
• Has not sustained any new fracture
• Walks three times a week, good calcium intake with diet
• Repeat BMD is stable
• No glucocorticoids, no kidney disease
• However...
Concerns with long-term use of bisphosphonates

• Osteonecrosis of the Jaw
• Atypical femur fractures
• Acute kidney injury
• Atrial fibrillation
• Esophageal cancer
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>- Sex</td>
<td>- Low BMI</td>
</tr>
<tr>
<td>- Age</td>
<td>- Parental history of fracture (especially hip)</td>
</tr>
<tr>
<td>- BMD</td>
<td>- Current smoking</td>
</tr>
<tr>
<td>- Fragility fracture after 40</td>
<td>- Alcohol intake ≥ 3 units/day</td>
</tr>
<tr>
<td>- Systemic glucocorticoid use (≥3 months)†</td>
<td>- 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
† ≥3 months in the prior year of a prednisone equivalent dose ≥ 7.5mg 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.

High risk (> 20%)

Hip / vertebral fracture

> 1 non-vertebral fragility fracture

*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?

First Line Therapies with Evidence for Fracture Prevention in Postmenopausal Women*

<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>

- **Bisphosphonates**
- **Denosumab**
- **Raloxifene**
- **Estrogen** *(Hormone therapy)*
- **Teriparatide**
- **Alendronate**
- **Risedronate**
- **Zoledronic Acid**

- **Vertebral**
- **Non-Vertebral**

+ 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, effectiveness and cost-effectiveness documented\(^1\)-\(^3\)
- 1\(^{st}\) line agents for treatment of patients at high risk for fragility fracture
  - Generally well tolerated
  - Low cost (generic formulation)

\(^3\) Langsetmo LA et al. *Osteoporos Int* 2009; 283-290
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

Bisphosphonates: good and bad?

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

• Presence of exposed bone in the maxillofacial region that does not heal within 8 weeks
• 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:
  – Withhold bisphosphonates for up to 3 months prior and until complete healing
  – www.osteoporosis.ca (healthcare professionals)
Atypical Femur Fractures

- Insufficiency fracture
- Associated with long term bisphosphonate use
- Infrequent

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

Shane E et al J Bone Miner Res. Epub 2013 May 28
Incidence of AFF

- Incidence estimated to be $^{1}$
  - 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 $^{2}$

$^{1}$Dell 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 prodromal 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 (e.g., 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

<table>
<thead>
<tr>
<th>EVENTS</th>
<th>INCIDENCE PER 100 000 PERSON-YEARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bis-ONJ*</td>
<td>1.03</td>
</tr>
<tr>
<td>Bis-AFF (8 y)†</td>
<td>78</td>
</tr>
<tr>
<td>Bis-AFF (2 y)†</td>
<td>2</td>
</tr>
<tr>
<td>Death by murder†</td>
<td>1.62</td>
</tr>
<tr>
<td>Fatal MVA‡</td>
<td>8.4</td>
</tr>
<tr>
<td>Major osteoporotic fracture in low-risk women‡</td>
<td>650</td>
</tr>
<tr>
<td>Major osteoporotic fracture in moderate-risk women‡</td>
<td>1600</td>
</tr>
<tr>
<td>Major osteoporotic fracture in high-risk women§</td>
<td>3100</td>
</tr>
</tbody>
</table>
How long should we keep patients on therapy?

• Question applies to bisphosphonate therapy
  – Because:
    • Rising incidence of rare, but serious adverse events associated with prolonged use
    • NOT because the medications stop working

• Patient’s risk for fracture
• Affinity of bisphosphonate for bone
Concept of Drug Holiday

- Alendronate data
- Risedronate data
- 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 and bone loss resumes rapidly
Duration of Bisphosphonate Therapy

<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 to 20%) Without recent Fxs</td>
<td>Between 5 and 7 years</td>
<td>1 to 3 years depending on bisphosphonate used Risedronate&lt; Alendronate&lt; Zoledronic Acid</td>
</tr>
<tr>
<td>High (&gt;20%) Recent Fxs, Hip or Vertebral Fxs</td>
<td>Do not stop therapy or switch to another class of agents</td>
<td>Monitor for adverse events</td>
</tr>
</tbody>
</table>

What should we Monitor during a Drug Holiday?

- Fractures and Falls
- Bone Turnover Markers
- BMD
- 10 year Fracture Risk (FRAX)
Should we monitor BMD or BTMs?

1McNabb et al. *J Clin Endocrinol Metab* 2014 Epub Aug 15
2Bauer DC et al *JAMA Intern Med* 2014; 174: 1126-34
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
Mrs. Roy

- Could consider stopping bisphosphonate for 2-3 years, but should re-evaluate and perform fracture risk assessment every year
- If new fracture: resume treatment
- If no fracture: observation or change treatment, mode of administration?
Mrs. Roy. What if...

- Vertebral or hip fracture?
- 2 Fragility fractures at other sites?
- Positive family history of hip fracture?
- Breast cancer at 52 yo and early menopause?
- Asthmatic with regular use of inhaled steroids and intermittent use of oral glucocorticoids?
- History of malabsorption?
Key Messages

- Use fracture assessment tools
- Avoid basing treatment decisions on BMD alone
- Use anti-osteoporosis medications only in patients at moderate and high risk for fractures
- Monitor adherence, tolerability, falls and 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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