Better Bones: Optimising Osteoporosis Management in Older Patients

Dr Karen Rothacker
Endocrinologist, Royal Perth Hospital
Outline

• Definition
• Screening
• Risk Factors
• Secondary Causes
• Management

• Denosumab vs. bisphosphonates including side effects
• Bisphosphonate drug holiday
MCQ 1

A 68 yr old man with a BMI of 19.6 kg/m² and a history of heavy alcohol and cigarette consumption presents for a routine health check. He has had three falls in the past six mths. You consider his bone health in addition to his cardiovascular risk.
Which of the following is false:

A. He should be counselled to reduce his alcohol consumption given its impact on bone density as well as falls risk.

B. His low body weight is a risk factor for low bone density and ensuring he is meeting nutritional requirements would be prudent.

C. He should have a BMD assessment and meets MBS rebatable indications.

D. Smoking is a risk factor for osteoporosis.

E. If his lowest BMD T-score is -2.5, measurement of FBC, U&Es, LFTs, thyroid function, calcium, PTH and vitamin D would be appropriate.
Comparing alendronate, risedronate, zoledronic acid and denosumab, which of the following statements is correct?
A. Denosumab is associated with greater gains in BMD and lower fracture risk compared with bisphosphonates.

B. Treatment with alendronate for 10 yrs reduces risk of hip fracture more than 5 yrs treatment with alendronate.

C. With denosumab discontinuation, BMD returns to close to baseline within 1 – 2 yrs.

D. With zoledronic acid discontinuation, BMD returns to close to baseline within 1 – 2 yrs.

E. Zoledronic acid can be safely used in those with Stage IV CKD.
A 75 yr old woman has a history of minimal trauma vertebral fracture and femoral neck BMD T-score of -2.6. In addition to lifestyle measures, calcium and vitamin D supplementation you recommend anti-resorptive therapy. She is worried about osteonecrosis of the jaw (ONJ).
Which of the following about ONJ is true:

A. If she temporarily discontinues bisphosphonates prior to any invasive dental procedure, she will not develop ONJ.

B. The risk of ONJ is lower with denosumab and this would be the preferred treatment for this patient.

C. ONJ affects only those patients receiving high dose anti-resorptive therapy as is prescribed in malignancy

D. Her risk of ONJ is <1% compared to her 15%+ risk of osteoporotic fracture over the next 10 years.

E. ONJ is associated with high morbidity and mortality.
Osteoporosis Definition

- Bone Density Criteria

<table>
<thead>
<tr>
<th>Condition</th>
<th>T-score</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>-1 or above</td>
</tr>
<tr>
<td>Osteopaenia</td>
<td>Between -1 and -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Below -2.5</td>
</tr>
</tbody>
</table>

- Minimal trauma fracture
  - Hip
  - Vertebra
  - Other sites: proximal humerus, distal radius, pelvis
Screening Bone Density – MBS Rebatable

- Age ≥70 years for women AND men
- Minimal trauma fracture
- Age ≥50 years and risk factor(s):
  - Glucocorticoid therapy (≥7.5mg daily of pred for ≥3months)
  - Chronic kidney or liver disease
  - Hypogonadism/early menopause
  - Primary hyperparathyroidism
  - Hyperthyroidism
  - Coeliac disease/malabsorption
  - Rheumatoid arthritis
Screening Bone Density – Non-Rebatable

- Age ≥50 years and risk factor(s):
  - Parental history of hip fracture
  - Recurrent falls
  - Breast cancer on aromatase inhibitor
  - Long-term treatment with anti-epileptic medications
  - Low body weight or history of restricted eating, i.e. anorexia
  - HIV and its treatment
  - Long-standing major depression/SSRI treatment
  - Diabetes (type 1 and type 2)
  - Organ or bone marrow transplant
Addressing Modifiable Risk Factors

• Lifestyle
  • Nutrition, especially calcium intake
  • Vitamin D insufficiency
  • Low body weight
  • Lack of weight bearing physical activity
  • Falls (muscle mass and strength, balance)
  • Smoking
  • Alcohol
Addressing Modifiable Risk Factors

- Medications – Is ongoing use required/can dose be reduced?
  - Glucocorticoids
  - Aromatase inhibitors/anti-androgen therapy
  - Anti-epileptics
  - SSRIs
  - PPIs
  - Tenofovir
<table>
<thead>
<tr>
<th>Consider Secondary Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hyperthyroidism*</td>
</tr>
<tr>
<td>• Hyperparathyroidism*</td>
</tr>
<tr>
<td>• Hypogonadism*</td>
</tr>
<tr>
<td>• Chronic inflammatory, kidney or liver disease</td>
</tr>
<tr>
<td>• Coeliac disease</td>
</tr>
<tr>
<td>• Myeloma</td>
</tr>
<tr>
<td>• HIV infection</td>
</tr>
<tr>
<td>• Cushing’s syndrome*</td>
</tr>
</tbody>
</table>

*Conditions which would warrant Endocrinology referral.
Other conditions may prompt referral to appropriate specialty

+Others but osteoporosis unlikely to be the only presenting feature
What Tests to Do?

- For all patients:
  - FBC
  - U&Es, LFTs
  - Thyroid function
  - Calcium and PTH
  - Vitamin D
What Tests to Do?

- Consider for unexplained osteoporosis (without risk factors) or Z-score >-2.0:
  - Coeliac serology
  - Serum and urine electrophoresis/serum free light chains
  - HIV serology
  - Post dexamethasone cortisol or 24 hour urinary free cortisol
  - Fasting, early morning testosterone in men
Who to Treat?

- History of minimal trauma fracture*
- T-score ≤-2.5 at either the femoral neck or spine*
- T-score between -1 and -2.5 at the femoral neck or spine and a 10 year probability of hip fracture ≥3% or any osteoporotic fracture ≥20%

Fracture risk calculators:

*PBS supported therapy for
- Minimal trauma fracture (any age), or
- 70 yrs+ and T-score ≤-2.5 (oral bisphosphonate or denosumab) or ≤-3.0 (zoledronic acid)
- Corticosteroid therapy (pred equivlal dose >7.5mg daily for ≥3mths) and T-score ≤-1.5
Management

• Non-Pharmacological
  • Preventative strategies, including calcium and vitamin D
  • Address falls risk
Management

- Pharmacological
  - Estrogen +/- progesterone (agen)
  - Raloxifene, Bazedoxifene, Tibolone
- Bisphosphonates
  - Oral (alendronate, risedronate)
  - Intravenous zoledronic acid
- Denosumab
  - Teriparatide

Considerations in post-menopausal women, generally within 10 years of menopause and with other menopausal symptoms or intolerant of other treatments.

Requires specialist prescription. Reserved for those at high fracture risk who are fracturing despite anti-resorptive therapy. Refer.
# Bisphosphonates vs Denosumab - Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Denosumab</th>
<th>Alendronate</th>
<th>Risedronate</th>
<th>Zoledronic acid</th>
</tr>
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<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Markers</td>
<td>↓↓↓</td>
<td>↓↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>BMD</td>
<td>↑↑↑</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>VFx</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓/↓↓</td>
<td>↓</td>
</tr>
<tr>
<td>Non-VFx</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓/↓↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Treatment duration</strong></td>
<td>Up to 10 yrs</td>
<td>Up to 10 yrs</td>
<td>Up to 7 yrs</td>
<td>Up to 9 yrs</td>
</tr>
<tr>
<td></td>
<td>FREEDOM</td>
<td>FLEX</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Anastasilakis, *Eur J Endo* 2018
## Bisphosphonates vs Denosumab – Residual Effect

<table>
<thead>
<tr>
<th></th>
<th>Denosumab</th>
<th>Alendronate</th>
<th>Bisphosphonates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bone Markers</strong></td>
<td>↑↑↑</td>
<td>↓</td>
<td>Return to baseline</td>
</tr>
<tr>
<td><strong>BMD</strong></td>
<td>↓↓↓</td>
<td>←</td>
<td>↓</td>
</tr>
<tr>
<td><strong>VFx</strong></td>
<td>Return to baseline</td>
<td>↓↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Non-VFx</strong></td>
<td>Return to baseline</td>
<td>←</td>
<td>Return to baseline</td>
</tr>
</tbody>
</table>

Return to baseline

*Multiple VFs in a minority of patients with discontinuation

Anastasilakis, Eur J Endo 2018
## Bisphosphonates vs Denosumab – Safety

<table>
<thead>
<tr>
<th>Safety</th>
<th>Denosumab</th>
<th>Alendronate</th>
<th>Risedronate</th>
<th>Bisphosphonates</th>
<th>Zoledronic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONJ</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Atypical femoral fractures</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>Myalgias/arthralgias Hypocalcaemia VFx with discontinuation</td>
<td>GI upset Nephrotoxicity</td>
<td>GI upset Nephrotoxicity</td>
<td>Infusion reactions Nephrotoxicity Hypocalcaemia ?AF</td>
</tr>
</tbody>
</table>

Anastasilakis, *Eur J Endo* 2018
Osteonecrosis of the Jaw

- Presence of exposed and necrotic maxillofacial bone that does not heal within 8 weeks
- Pathogenesis unclear
- Rare event, incidence ~1–90 cases per 100,000 pt-yrs (marginally higher than the general population).
- Denosumab ≈ Bisphosphonates
Atypical Femoral Fractures

- Fracture below the lesser trochanter of the femur. May have prodromal dull or aching pain in groin or thigh.
- **Rare** event, incidence ~ 3–50 cases per 100,000 pt-yrs.
- Denosumab ≈ Bisphosphonates
- ↑Risk with prolonged treatment, risk declines following discontinuation.
Denosumab Discontinuation

• BMD accrued with treatment rapidly declines (12 mths) with ↑bone turnover markers above pre-treatment levels
• Suggestion of ↑risk of multiple vertebral fractures
• BMD loss can be attenuated by bisphosphonate therapy and teriparatide.

Tsourdi, Bone 2017
Bisphosphonate Drug Holiday

• Rationale
  • Increased duration of use is associated with:
    • Plateau in BMD increase
    • No additional reduction in nonVFx (alendronate – FLEX and zoledronic acid – HORIZON).
    • Increase risk of atypical femoral fractures
    • Long durability of effect
Bisphosphonate Drug Holiday

• Re-evaluate fracture risk after 5 yrs of oral bisphosphonate or 3 yrs of zoledronic acid use. Treatment cessation in those not at high risk at fracture.
• Monitor clinically and with BMD and bone turnover.
• Re-initiate therapy (bisphosphonate or denosumab) if new fracture, significant decline in BMD or ↑ in bone turnover.
MCQ 1

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E. ONJ is associated with high morbidity and mortality.
References

• Health Pathways. https://wa.healthpathways.org.au


Questions??
Fracture Risk Calculators

• FRAX –
  www.sheffield.ac.uk/FRAX/tool.aspx?country=31

• Garvan –
Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

<table>
<thead>
<tr>
<th>Questionnaire:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age (between 40 and 90 years) or Date of Birth</td>
</tr>
<tr>
<td>Age: 75</td>
</tr>
<tr>
<td>Date of Birth:</td>
</tr>
<tr>
<td>2. Sex</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>3. Weight (kg)</td>
</tr>
<tr>
<td>57.8</td>
</tr>
<tr>
<td>4. Height (cm)</td>
</tr>
<tr>
<td>170</td>
</tr>
<tr>
<td>5. Previous Fracture</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>6. Parent Fractured Hip</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>7. Current Smoking</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>8. Glucocorticoids</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>9. Rheumatoid arthritis</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>10. Secondary osteoporosis</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>11. Alcohol 3 or more units/day</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>12. Femoral neck BMD (g/cm²)</td>
</tr>
<tr>
<td>T-Score</td>
</tr>
</tbody>
</table>

BMI: 20.0
The ten year probability of fracture (%) with BMD
Major osteoporotic: 15
Hip Fracture: 6.5

If you have a TBS value, click here: Adjust with TBS
Garvan

**FRACUTRE RISK CALCULATOR**

Please help Garvan continue its research into osteoporosis. Visit http://www.garvan.org.au/osteoporosis to donate now

<table>
<thead>
<tr>
<th></th>
<th>5 &amp; 10 year Fracture Risk For</th>
<th>Prepared 23-Aug-19</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hip Fracture</td>
<td>Any Osteoporotic / Fragility Fracture</td>
</tr>
<tr>
<td>%</td>
<td>5 year risk</td>
<td>10 year risk</td>
</tr>
<tr>
<td>9%</td>
<td>17%</td>
<td>21%</td>
</tr>
</tbody>
</table>

The following values are equivalent to those at which current Pharmaceutical Benefits Scheme reimbursements for osteoporosis therapy apply.

<table>
<thead>
<tr>
<th></th>
<th>Hip Fracture</th>
<th>Any Osteoporotic / Fragility Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-5%</td>
<td>8-13%</td>
</tr>
<tr>
<td>Sex</td>
<td>3-9%</td>
<td>14-26%</td>
</tr>
<tr>
<td>Age</td>
<td>5 year risk</td>
<td>5 year risk</td>
</tr>
<tr>
<td>Fractures since age of 50</td>
<td>10 year risk</td>
<td></td>
</tr>
<tr>
<td>Falls over last 12 months</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>T-Score</td>
<td>-2.6</td>
<td>Not Provided</td>
</tr>
<tr>
<td>Actual BMD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fracture Risk Calculators

- **FRAX**
  - Doesn’t factor in magnitude of contributing risks
  - Doesn’t consider falls risk
- **Garvan**
  - Doesn’t consider as many risk factors as FRAX
- **Neither consider**
  - Bone turnover markers
  - Change in bone density over time