Update in Management of Osteoporosis

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Malaysia is ageing

According to the Population Projections (Revised) 2010-2040 prepared by the Department of Statistics, Malaysia is expected to become an ageing nation by the year 2020 when the percentage of those aged 65 years and above reaches 7.2 per cent, while the fertility rate continues to drop below the replacement level of 2.1.

The report also reveals that Malaysia will be an aged population by the year 2040 when those aged 65 years and above reach 14.5 per cent, drawing nearer to the percentage of those aged 14 years and below, which will be at 18.6 per cent.

The department’s chief statistician, Datuk Seri Dr Mohd Uzir Mahidin, explains that as the percentage of those aged 65 and above continues to increase due to higher life expectancy, the percentage of the working population that can contribute to the country’s economic development will decline.

### Life Expectancy

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 14 yrs</td>
<td>27.4%</td>
<td>18.6%</td>
<td>67.6%</td>
</tr>
<tr>
<td>15 - 64 years</td>
<td>72.2%</td>
<td>61.6%</td>
<td>65.4%</td>
</tr>
<tr>
<td>&gt; 65 yrs</td>
<td>5.0%</td>
<td>70.0%</td>
<td>74.7%</td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2040</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Note: Provided by the Department of Statistics Malaysia
Osteoporosis

- Consequences of Fragility fracture / non-adherence
- Drop in Diagnosis / Treatment .. FEAR!
- Beyond Fracture reduction ...
- Fracture efficacy: Anabolic vs Anti-resorptive
- Discontinuation of Denosumab – effects
- When to STOP? When to SWITCH?
- A Call to Action!
What to EXPECT after a Fracture?

Highest risk of Re-Fracture is within next 1-2 yrs
Risk of Another Vertebral Fracture is Higher in the Year Following a New Fracture

- Overall, ~20% fractured again within 1 year following a new fracture
- Risk of fracture increased with the number of baseline fractures

*\( p<0.05, \text{ vs patients with no prevalent vertebral fractures (12-fold increased risk)} \)

Dilemma: Do Risks outweigh Benefits

- Anti-fracture efficacy
- Long term safety
Hidden Fissures: Hip Fracture Rates End Years-Long Decline

BY ERIC SEABORG | MAY 2017

Data source: Medical Expenditure Panel Survey (MEPS).
Fearing Drugs’ Rare Side Effects, Millions Take Their Chances With Osteoporosis

June 2, 2016 | NOF in the News, Osteoporosis in the News

Millions of Americans are missing out on a chance to avoid debilitating fractures from weakened bones, researchers say, because they are terrified of exceedingly rare side effects from drugs that can help them. Last month, the American Society for Bone and Mineral Research, the National Osteoporosis Foundation and the National Bone Health Alliance put out an urgent call for doctors to be more aggressive in treating patients at high risk, and for patients to be more aware of the need for treatment. Read about the conversation in this New York Times article.

“Ninety percent of patients, when you talk to them about starting one of these drugs, won’t go on,” said Dr. Paul D. Miller, medical director of the Colorado Center for Bone Research, a medical practice in Lakewood. “Ninety percent who are on the drugs want to come off. The fear factor is huge.”
Adherence and Fracture reduction
Persistence with Oral anti-osteoporosis treatments is generally poor

Note: Databases are not designed to follow up persistence with treatment. They do not confirm that patients take the medication, and data can be inaccurate. A random sample (10%) of adult male and female patients who initiated osteoporosis treatment between 1 Dec 2010 – 30 Jun 2014 were included in the analysis. Non-persistence defined as 90 days in the follow-up period without a filled prescription.

Medicare Australia database (DHS M14118) 1. Maclean A et al. Presented at ANZBMS Nov 2015, Australia
Consequence of NOT TAKING medication ...
Fracture Risk in patients with $\leq 50\%$ persistence is the same as in patients who take no medication at all

Based on study of 35,537 patients from 2 US claims database.

*MPR (medication possession ratio) measures refill compliance

Beyond Fracture reduction ...
Zole: Effect on All-Cause Mortality Over Time

Hazard ratio, 0.72 (95% CI, 0.56–0.93)
P = .0117

Absolute Risk Reduction 3.7%

## Reduced Mortality with Osteoporosis Treatments

### Study and Treatment Details

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Relative Risk [95% CI]</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris 1999</td>
<td>Aln</td>
<td>0.94 [0.47, 1.89]</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Reginster 2000</td>
<td>Aln</td>
<td>0.65 [0.31, 1.36]</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>McClung 2001</td>
<td>Zole</td>
<td>0.90 [0.71, 1.16]</td>
<td>18.5</td>
<td></td>
</tr>
<tr>
<td>Meunier 2004</td>
<td>Strontium</td>
<td>1.36 [0.78, 2.37]</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>Reginster 2005</td>
<td>Strontium</td>
<td>0.88 [0.71, 1.10]</td>
<td>23.6</td>
<td></td>
</tr>
<tr>
<td>Black 2007</td>
<td>Zole</td>
<td>1.16 [0.90, 1.48]</td>
<td>18.4</td>
<td></td>
</tr>
<tr>
<td>Lyles 2007</td>
<td>D’mab</td>
<td>0.72 [0.56, 0.91]</td>
<td>19.6</td>
<td></td>
</tr>
<tr>
<td>Cummings 2008</td>
<td>D’mab</td>
<td>0.78 [0.57, 1.06]</td>
<td>11.9</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>0.89 [0.80, 0.99]</strong></td>
<td><strong>P=0.036</strong></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $I^2 = 37\%$, $P = 0.14$

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MJ Bolland et al. *Journal of Clinical Endocrinology & Metabolism* 2010, 95, 1174-1181
Alendronate Rx → ↓risk of hip fracture

- crude HR 0.62 (0.49–0.79), P < 0.001
- multivariable models HR 0.66 (0.51–0.86), P < 0.01

Alendronate was related to reduced mortality risk

HR 0.88 (0.82–0.95)

NNT to prevent 1 hip # = 26

Anabolic vs Anti-resorptive...
Effects of Teriparatide vs Risedronate on New fractures in PMO (VERO Study) – an RCT

Incidence of NEW Vertebral fracture

Relative risk: 0.52
(95% CI: 0.30–0.91)
p = 0.019

Denosumab – effects of Drug withdrawal
Denosumab and bisphosphonates work differently

- Denosumab blocks osteoclast formation, function
- BPs cause loss of resorptive function but
- BPs bind to bone mineral at sites of bone turnover

RANK L
RANK
OPG
Denosumab
BP = bisphosphonate
Denosumab and Fracture Risk Analyses in Patients Age 75 and Older

Pre-planned

- Placebo
- Denosumab

Incidence at Month 36 (%)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Vertebral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>68%</td>
<td>64%</td>
</tr>
<tr>
<td>(59%, 74%)</td>
<td>47%, 75%</td>
<td></td>
</tr>
<tr>
<td>$P &lt; 0.001$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Effects of Denosumab Treatment on Lumbar Spine BMD and New Vertebral Fractures Through 10 Years

Placebo  Long-term Denosumab  Cross-over Denosumab

Lumbar Spine

FREEDOM Extension

21.7% c

16.5% c

Percentage Change From Baseline

Study Year

0 1 2 3 4 5 6 7 8 9 10

-2 0 2 4 6 8 10 12 14 16 18 20 22 24

BMD data are LS means and 95% confidence intervals. aP < 0.05 vs FREEDOM baseline. bP < 0.05 vs FREEDOM and Extension baselines. cPercentage change while on denosumab treatment. dAnnualized incidence: (2-year incidence) / 2. Lateral radiographs (lumbar and thoracic) were not obtained at years 4, 7, and 9 (years 1, 4, and 6 of the Extension).

Bone et al., Lancet Diabetes Endocrinol 2017
BMD Changes over the long term (5-10 yrs)

**Total Hip**

- FREEDOM
- Extension
  - 9.2%
  - 7.4%

**Graphs**

- ALN/Placebo
- ALN/ALN (Pooled 5 mg and 10 mg groups)

**Mean Percent Change**

- P<0.001

**Percentage Change (%)**

- ZOL
- ZOL/PBO
  - +4.3%
  - +2.8%

**Study Year**

- 0 1 2 3 4 5 6 7 8 9 10

**Month**

- 0 12 24 36 48 60 72 84 96 108 120

**Time (Years)**

- 0 1 2 3 4 5 6

*Black, JAMA 2006*

*Black, JBMR 2012*
Effects of 1-year Follow-up Observational Phase After 8 Years of Continued DMAb Treatment on Lumbar Spine BMD

- **Placebo**
- **Denosumab**
- **Observation**

**Parent Study**

**Extension Study**

*All on DMAb Treatment*  
*Observation*

- **N = 52**  
  - 16.8%  
  - 8.1%  

- **N = 10**  
  - 6.7%  
  - 5.1%

Includes subjects who enrolled into the observational phase with 8 years of continued DMAb treatment (N = 52) or those with 4 years of placebo followed by 4 years of continued DMAb treatment (N = 10).

McClung et al., Osteoporosis Int 2017
Bone turnover markers 7 to 24m after denosumab discontinuation in patients previously treated or not with BPs

Uebelhart et al. Osteoporos Int 2017
Percent Change in Lumbar Spine & Total Hip BMD

**DAPS Study**

Analysis of BMD measurements were exploratory, and not powered to study a true difference. An ANCOVA model for each treatment period was used to calculate the percent change from Month 12 to Month 24 (indicated in gold). The period baseline value of the variable, treatment, machine type, period baseline value by machine type interaction was separately adjusted and stratified by center and prior osteoporotic fracture.

ALN=alendronate; ANCOVA=analysis of covariance; BMD=bone mineral density; DAPS=Denosumab Adherence Preference Satisfaction

**Bisphosphonates**
for 3 yrs (IV BPs)
for 5 yrs (Oral BPs)

**LOW risk**
- Consider Drug holiday
- Reassess every 2-3 years

**HIGH* risk**
- Consider Switch to TPT or D’mab

*HIGH risk:*
- Hip, spine or multiple fractures before or during therapy
- Femoral neck BMD < -2.5 (T-score), if age <65 yrs; T score < -2.0, in >65 yrs; or frequent falls
- Continuing hormone ablative therapy
- 2° osteoporosis, continuing glucocorticoid therapy

**WHEN TO STOP? WHEN TO SWITCH?**

Swiss guidelines, 2017
Meier et al, in press
WHEN TO STOP? WHEN TO SWITCH?

SERMs For 3-5 years

LOW risk
Consider Drug holiday
Reassess every 2-3 years

HIGH* risk
Consider Switch to BP / D’mab

*HIGH risk:
- Hip, spine or multiple fractures before or during therapy
- Femoral neck BMD < -2.5 (T-score), if age <65 yrs; T score < -2.0, in >65 yrs; or frequent falls
- Continuing hormone ablative therapy
- 2⁰ osteoporosis, continuing glucocorticoid therapy

Swiss guidelines, 2017
Meier et al, in press
WHEN TO STOP? WHEN TO SWITCH?

Denosumab
For 4-5 years

LOW risk
- No Drug holiday
  - But SWITCH to BPs for 12-24 months

HIGH* risk
- Consider continue Dmab or add TPT

*HIGH risk:
- Hip, spine or multiple fractures before or during therapy
- Femoral neck BMD < -2.5 (T-score), if age <65 yrs; T score < -2.0, in >65 yrs; or frequent falls
- Continuing hormone ablative therapy
- 2° osteoporosis, continuing glucocorticoid therapy

Swiss guidelines, 2017
Meier et al, in press
Teriparatide for 2 years

No Drug holiday

But

SWITCH to BPs or D’mab

Sequential therapy

HIGH risk

Swiss guidelines, 2017
Meier et al, in press

WHEN TO STOP?
WHEN TO SWITCH?
Sneak Peak ...

Romosozumab

Romosozumab Is a Humanized Monoclonal Antibody That Binds and Inhibits Sclerostin
When to Treat & with What?

- Despite availability of effective anti-osteoporosis therapies, LOW proportions of patients treated
- Teriparatide more effective vs risedronate
- Problem identified with denosumab --- rapid loss of efficacy with consequent vertebral fracture risk returning to placebo level (Don’t stop, transition to bisphosphonate)
- Exciting NEW modality → (Romosozumab)
- Underestimated / under-diagnosed / under-treated

UNDERTAKER !?
A Call to Action!

• 1 in 2 older women & 1 in 3 older men will suffer an osteoporotic fracture
• Will fracture again
• Can DIE ... Will DIE

Missed Opportunity

J Eisman, 2015 AFOS