Current Treatment Options for Osteoporosis

An update

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Current treatment options

- Overview of choices for prescribers
- Strontium update
- Denosumab
- Calcium and vitamin D3
- How long to treat?
Attributes to be considered

- Evidence-based efficacy
- Clinical effectiveness
  - Low NNTs
- Fracture rate reduction at specific sites
  - Hip
  - Vertebral
  - Non-hip, non-vertebral
- Speed of onset and offset of effect
- Acceptability, including dosing instructions and periodicity
- Safety, side effects, interactions
  - Short-term
  - Long-term
- Cost effectiveness
Time dependency of re-fracture

4140 post menopausal women age 50-90

23% re-fractures
54% re-fractures

First fracture
Second fracture

Treatments

- Bisphosphonates
  - Etidronate (daily)
  - Alendronate (weekly)
  - Risedronate (weekly)
  - Ibandronate (monthly or IV three monthly)
  - Zoledronate (IV annually)
- Raloxifene – a SERM (daily)
- Strontium ranelate (daily) ???
- Denosumab – monoclonal antibody to RANK ligand (subcutaneous 6 monthly)
- Parathyroid hormone – an anabolic agent (s/c, daily for 2 years)
Effect on vertebral fractures: risk reduction

Summary of pivotal trials: not a head-to-head study

Fracture risk reduction (%)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fracture Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>-48%</td>
</tr>
<tr>
<td>Risedronate</td>
<td>-36%</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>-59%</td>
</tr>
<tr>
<td>Etidronate</td>
<td>-40%</td>
</tr>
<tr>
<td>Strontium</td>
<td>-41%</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>-40%</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>-70%</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>-65%</td>
</tr>
<tr>
<td>Denosumab</td>
<td>-68%</td>
</tr>
</tbody>
</table>

ORAG. *Endocrine Rev* 2002
Meunier, P. J. et al *N Engl J Med*
Cummings SR et al (2009) *NEJM*
Effect on hip fracture risk reduction

Summary of pivotal trials: not a head-to-head study


*post hoc analysis
Effect on non-vertebral fractures

Summary of pivotal trials: not a head-to-head study

-28%* -12% -33% -39%* -20%* -2% -25%* -53%* -16%* -20%*

Fracture risk (%)

Alendronate FIT 1
Alendronate FIT 2
Risedronate VERT MN
Risedronate VERT NA
Ibandronate Hip
Zoledronate
Teiparaide 20 mg
Strontium
Denosumab
Adjusted fracture relative risk for persistent versus discontinued bisphosphonate users

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Relative Risk</th>
<th>Current Use</th>
<th>Fractures (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporotic</td>
<td>0.85</td>
<td>0.78</td>
<td>2029</td>
</tr>
<tr>
<td>Hip/femur</td>
<td>0.78</td>
<td>0.66</td>
<td>628</td>
</tr>
<tr>
<td>Hip femur*</td>
<td>0.66</td>
<td>0.77</td>
<td>247</td>
</tr>
<tr>
<td>Vertebra</td>
<td>0.77</td>
<td>1.04</td>
<td>372</td>
</tr>
<tr>
<td>Radius/ulna</td>
<td>1.04</td>
<td>0.92</td>
<td>590</td>
</tr>
<tr>
<td>Humerus</td>
<td>0.92</td>
<td></td>
<td>354</td>
</tr>
</tbody>
</table>

* More than 24 months persistence
Are we treating the right populations?

<table>
<thead>
<tr>
<th></th>
<th>osteoporotic</th>
<th>hip/femur</th>
<th>Hip femur*</th>
<th>Vertebra</th>
<th>radius/ulna</th>
<th>Humerus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident rate past</td>
<td>2.47</td>
<td>0.76</td>
<td>0.76</td>
<td>0.47</td>
<td>0.62</td>
<td>0.36</td>
</tr>
<tr>
<td>users (100 py)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;Baseline&quot; 10 year #</td>
<td>0.247</td>
<td>0.076</td>
<td>0.076</td>
<td>0.047</td>
<td>0.062</td>
<td>0.036</td>
</tr>
<tr>
<td>risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated incident</td>
<td>2.35</td>
<td>0.7</td>
<td>0.54</td>
<td>0.41</td>
<td>0.68</td>
<td>0.41</td>
</tr>
<tr>
<td>rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARR/year</td>
<td>0.12</td>
<td>0.06</td>
<td>0.22</td>
<td>0.06</td>
<td>-0.06</td>
<td>-0.05</td>
</tr>
<tr>
<td>NNT/year</td>
<td>833</td>
<td>1667</td>
<td>455</td>
<td>1667</td>
<td>-1667</td>
<td>-2000</td>
</tr>
</tbody>
</table>

* More than 24 months persistence

Adapted from Gallacher AM et al. Fracture Outcomes related to persistence and compliance with oral bisphosphonates. JBMR (2008) On line first
Highest Absolute risk means lowest numbers needed to treat

<table>
<thead>
<tr>
<th></th>
<th>60-64</th>
<th>65-69</th>
<th>70-74</th>
<th>75-79</th>
<th>80-84</th>
<th>&gt;85</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients</td>
<td>168,729</td>
<td>114,927</td>
<td>88,393</td>
<td>64,959</td>
<td>43,032</td>
<td>32,559</td>
<td>512,599</td>
</tr>
<tr>
<td>Expected Hip Fx</td>
<td>90</td>
<td>165</td>
<td>180</td>
<td>445</td>
<td>703</td>
<td>961</td>
<td>2,544</td>
</tr>
<tr>
<td>Actual Hip Fx</td>
<td>76</td>
<td>121</td>
<td>172</td>
<td>273</td>
<td>345</td>
<td>587</td>
<td>1,574</td>
</tr>
<tr>
<td>Saved Hip Fx</td>
<td>14</td>
<td>44</td>
<td>8</td>
<td>172</td>
<td>358</td>
<td>374</td>
<td>970</td>
</tr>
</tbody>
</table>

NNT = 87

NNT = 12,052

Data from SCAL Healthy Bones Programme: used with kind permission Rick M Dell MD
Strontium ranelate
Hip Fracture prevention with strontium

*TROPOS trial and high risk patients (≥ 74 years, T-score ≤ −3)*

**RRR = 15%**

**P = NS**

<table>
<thead>
<tr>
<th>Risk of Hip Fracture</th>
<th>Overall (ITT population)</th>
<th>n= 2479</th>
<th>n= 2453</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RRR = 15%</td>
<td>P = NS</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk of Hip Fracture</th>
<th>High risk *</th>
<th>n=996</th>
<th>n= 982</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RRR 36%</td>
<td>(41%, 99.7%)</td>
<td>P = 0.046</td>
</tr>
</tbody>
</table>

*Higher risk patients defined as: age ≥ 74 years and a femoral neck T-score of ≤ -3

Integrated analysis – reduced vertebral fracture risk in patients over 80 years

ITT, over 3 years: RR = 0.68; 95% CI [0.50; 0.92] *p=0.013
Semi-quantitative assessment, Kaplan-Meier, Cox Model
Strontium reduces fracture risk in patients >80 years in 1\textsuperscript{st} year

Vertebral fractures

\begin{itemize}
  \item Placebo: 8.3% (RRR 59%)
  \item Strontium 2 g/day: 3.5%
\end{itemize}

\[ \text{ITT, RR=0.41, 95\% CI [0.22; 0.75]} \]
\[ N=895 \]

Non-vertebral fractures

\begin{itemize}
  \item Placebo: 6.8% (RRR 41%)
  \item Strontium 2 g/day: 4.0%
\end{itemize}

\[ \text{ITT, RR=0.59, 95\% CI [0.37; 0.95]} \]
\[ N=1488 \]

\[ p=0.002 \]
\[ p=0.027 \]

Strontium ranelate: EMA warnings

- The PRAC: for every 1,000 patient-years there were
  - 4 more cases acute coronary events
  - 4 more cases of thrombo-embolic events than with placebo
  - other risks, such as serious skin reactions, disturbances in consciousness, seizures (fits), liver inflammation and reduced number of blood cells.

- Still available but contraindicated with current or past h/o IHD, PAD, cerebrovascular disease, uncontrolled hypertension
Denosumab
Excess RANK Ligand can increase bone resorption, leading to osteoporosis

- CFU-GM
- Prefusion Osteoclast
- Bone Formation
- Osteoblasts
- Bone Resorption
- Bone

Decreased Oestrogen leads to increased RANK Ligand

- Multinucleated Osteoclast
- Activated Osteoclast

Denosumab binds RANK Ligand and inhibits osteoclast formation, function, and survival

Osteoclast Formation, Function, and Survival Inhibited

Bone Formation

Bone Resorption Inhibited

Denosumab 60mg s/c twice yearly
Effect on vertebral and non-vertebral fractures

3 year FREEDOM trial (7808 women mean age 72.3)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>Denosumab 60mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>New vertebral fracture</td>
<td>2.3</td>
<td>0.7</td>
</tr>
<tr>
<td>New non-vertebral fracture</td>
<td>6.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>8.0</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Mean F/N T score -2.2
Mean L/S T score -2.8
24% prevalent VCF

Effect of denosumab on wrist fractures

FREEDOM Trial

The effect of denosumab on new vertebral fractures over time

Time to first hip fracture with denosumab

40% RRR at 3 years (95% CI 0.37, 0.97) \( p = 0.04 \)

<table>
<thead>
<tr>
<th>Number of patients at risk</th>
<th>Placebo, n</th>
<th>3,906</th>
<th>3,799</th>
<th>3,672</th>
<th>3,538</th>
<th>3,430</th>
<th>3,311</th>
<th>3,221</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denosumab, n</td>
<td>3,902</td>
<td>3,796</td>
<td>3,676</td>
<td>3,566</td>
<td>3,477</td>
<td>3,397</td>
<td>3,311</td>
<td></td>
</tr>
</tbody>
</table>
Hip Fracture Prevention in Over 75s with denosumab

FREEDOM Trial – Subgroup analysis

In a subset of higher risk patients age ≥ 75 years

Post-Hoc Analysis‡
Age ≥ 75 years

RRR = 62%
(22%, 82%)
P = 0.007

RRR = 40%
(37%, 97%)
P = 0.04

Incidence at Month 36 (%)
Risk Reduction in Vertebral Fracture at 36 Months by Baseline CrCl

- **Denosumab (N=3902)**
- **Placebo (N=3906)**

<table>
<thead>
<tr>
<th>CrCl Range</th>
<th>Denosumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 – 29 mL/min</td>
<td>7.2</td>
<td>9.1</td>
</tr>
<tr>
<td>30 – 59 mL/min</td>
<td>7.0</td>
<td>9.1</td>
</tr>
<tr>
<td>60 – 89 mL/min</td>
<td>7.0</td>
<td>7.0</td>
</tr>
<tr>
<td>≥ 90 mL/min</td>
<td>8.1</td>
<td>8.1</td>
</tr>
</tbody>
</table>

- *P < 0.05*

**Percent Incidence at Month 36**

- **N = number of randomised subjects.**
- **N1 = number of randomised subjects with an evaluation during the time period of interest.**
- There were no subjects with a CrCl < 15 mL/min. *P < 0.05

Long-term denosumab data - Extension Study Design

International multicentre, open-label, single-arm Study

FREEDOM Study
N = 7808

EXTENSION Study
N = 2207
(De Novo
received placebo in FREEDOM)

N = 2343
(Long Term
received denosumab in FREEDOM)

DMAB 60 mg SC Q6M

Calcium and Vitamin D

0 1 2 3 4 5 10
Years

Summary of Serious Adverse Events over 3 & 5 Years
FREEDOM + Extension Study

<table>
<thead>
<tr>
<th></th>
<th>FREEDOM Placebo N = 3883 Rate (Event)</th>
<th>FREEDOM DMAB N = 3879 Rate (Event)</th>
<th>EXTENSION DMAB Long-Term N = 2343 Rate (Event)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Adverse Events*</td>
<td>10.4</td>
<td>10.6</td>
<td>10.8</td>
</tr>
<tr>
<td>Infections</td>
<td>1.3 (134)</td>
<td>1.5 (160)</td>
<td>1.2 (55)</td>
</tr>
<tr>
<td>Cellulitis or Erysipelas</td>
<td>&lt; 0.1 (1)</td>
<td>0.1 (12)</td>
<td>&lt; 0.1 (3)</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atypical fracture</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Rate per 100-Patient-Years

2 subjects had AE adjudicated to ONJ in the group that received placebo followed by denosumab

Calcium and vitamin D3
What do we know?

- All pivotal trials included calcium/D3 co-prescription
- Calcium/D3 reduces fractures in elderly in RNCH setting
- The evidence for calcium and/or D3 alone reducing fractures or falls is discrepant
- The evidence for calcium +/- D3 causing CVD or CVD related mortality is also discrepant
So what’s to do?

- Target CaD supplementation at those at high risk of fracture (and ? falls) and those with a high risk of insufficiency
  - elderly frail, house-bound and institutionalised
  - those with osteoporosis and fracture
  - those on bone-sparing agents
  - those on steroids
- modulate calcium insufficiency with diet if possible
- Use words like “ensure patient is replete with calcium and D3 with supplementation if necessary”
- Perhaps 1400 mg total threshold for calcium \(^1\)?

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Current controversies continue ..... how long to treat?

What are the risks?
Safety issues

- Osteonecrosis of the jaw
- Atypical femoral fractures
- Carcinoma of the oesophagus?
- Atrial fibrillation?
Osteonecrosis of the jaw
Atypical femoral fracture
Algorithm for long-term treatment

- **Recurrent fracture(s) Prevalent vertebral fracture(s) **

- **Advise 3-5 years treatment (Follow up at 3/12 to discuss treatment issues)** *

- "Above NOGG intervention threshold or hip BMD ≤ -2.5"
  - Check adherence, exclude secondary causes, re-evaluate treatment choice, continue treatment

- "Below NOGG intervention threshold and hip BMD ≥ -2.5"
  - Consider drug holiday
  - Repeat FRAX + BMD in 1.5-3 years

- "No new fracture"

* 3 years for zoledronate
  5 years for other BPs

** with oral BPs consider continuing if
- Age > 75
- Previous hip fracture
- Current GCs ≥ 7.5mg/d prednisolone

Adapted from http://www.shef.ac.uk/NOGG/NOGG_Executive_Summary.pdf
In summary

- No treatment abolishes all fractures!
- Some treatments are better at some sites than others
- Strontium use is restricted by safety concerns
- Denosumab is a recently introduced therapy with great promise and some distinctive properties
- Treatments need to be provided for those at highest risk
- Treatments need to be persisted with
- There are rare but likely harms from long term treatment therefore therapy holidays need to be considered
Thank you