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Background

Good evidence for 5 years bisphosphonate (BP) treatment\(^1\) but beyond this less clear
- BP long half-life; stopping treatment \(\rightarrow\) wears off gradually\(^2\)

Potential for harm
- Atypical fractures, osteonecrosis of the jaw (ONJ)
- Rare occurrence, \(\uparrow\) risk with increasing duration\(^3\)

BPs impair Bone Turnover; CTX bone turnover marker (bone resorption)
- Start BP \(\rightarrow\) ↓CTX
- Stop BP \& CTX rises\(^2\)

Drug holidays increasingly common - stop BP for period of time
Local practice since late 2012
- Review BP after 5 yrs
- Drug holiday
- Routine monitoring CTX at baseline, 4 months and 12 months

Our aim was to analyse changes in CTX on stopping long term bisphosphonate treatment to guide clinical decision-making on the duration of treatment cessation

Methods

- Patients on BP drug holiday via outpatient Bone Clinic identified from monitoring records
- Data extracted; patient age, sex, serum CTX levels 0, 4, 12 months, bisphosphonate and duration of use
- Excluded if baseline (0m) CTX \(\geq 0.51\) mg/L (higher fracture risk)
- Data analysis using Stata Statistics software.
- Offset of action defined as
  - a rise by the Least Significant Change (LSC=33%) in CTX and CTX above the pre-menopausal mean (0.13ug/L)

\[^*\]=2.33x\(\sqrt{\text{CV}^2}\)=\(\text{CV}^2\). \(\text{CV}\) is analytical coefficient of variation, \(\text{CVi}\) is intra-individual \(\text{CV}\)

Results

Overall population (figure 2):
- Detectable rise in CTX seen from as early as 4 months in 47% patients; 69% at 12 months

Subpopulations (figure 3):
- If CTX ≤ pre-menopausal mean (i.e. treatment target) at baseline, statistically significant increases in CTX seen at 4 and 12 months
  - If CTX > pre-menopausal mean at baseline, no significant change at 4 months, significant by 12 months
  - No significant difference between Alendronic acid and Risedronate seen (data not shown)

Monitoring outcomes using population data (figure 4):
- Baseline CTX not suppressed to premenopausal mean level after 5 yrs of BP use in 32% patients
- Where CTX suppressed at baseline:
  - At 4 months 28% had significant rise in CTX that was also above mean level (consider re-start)
  - At 12 months this had risen to 53%; 47% CTX still suppressed at this stage

Figure 1: All patient characteristics

<table>
<thead>
<tr>
<th>Median Patient Age</th>
<th>75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>83% female; 17% male</td>
</tr>
<tr>
<td>Mean Duration BP</td>
<td>8 years (range 3-15 years)</td>
</tr>
<tr>
<td>Alendronic acid</td>
<td>59%</td>
</tr>
<tr>
<td>Risedronate</td>
<td>33%</td>
</tr>
<tr>
<td>Other Bisphosphonate</td>
<td>8%</td>
</tr>
</tbody>
</table>

Total Patients = 158

Figure 4: CTX monitoring outcomes at baseline, 4 and 12 months

<table>
<thead>
<tr>
<th>4 month Review</th>
<th>N</th>
<th>Review (32%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTX ≤ pre-menopausal mean*</td>
<td>(68%)</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Delay restart (72%)</td>
<td></td>
</tr>
<tr>
<td>Consider restart (28%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>12 month Review</th>
<th>N</th>
<th>Delay restart (47%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTX suppressed?</td>
<td>N</td>
<td>Consider restart (53%)</td>
</tr>
</tbody>
</table>

\(*\text{Mean premenopausal CTX} \approx 0.19\)ug/L(0.05-0.63)\(^4\)

References


Conflicts of interest: None declared

Conclusion

- After at least 5 years of treatment, CTX may not be adequately suppressed in a third of patients. Drug adherence and therapy choice should be reviewed in this group.
- Less significant changes in CTX seen if levels not adequately suppressed at baseline? adherence
- Treatment effects can wear off as quickly as 4 months, but may also be maintained for 12 months
- Monitoring of CTX can potentially be used to identify these patients, some of whom may need to re-start treatment earlier

Figure 2: CTX at 0, 4, 12 months all patients

\(<\text{0.51 at baseline}\)