Can bone turnover markers help to define the duration of bisphosphonate drug holidays?
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Background

Good evidence for 5 years bisphosphonate (BP) treatment1,2 but beyond this less clear
- BP long half-life; stopping treatment wears off gradually2
Potential for harm
- Atypical fractures, osteonecrosis of the jaw (ONJ)
- Rare occurrence, ↑ risk with increasing duration3

BPs impair Bone Turnover; CTX bone turnover marker (bone resorption)
- Start BP → ↓ CTX
- Stop BP & CTX rises2

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 ≥0.51 ug/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 (0.19ug/L)

*1.233x(√CVa^21)+0.01ug/L (95%CI 0.00-0.02)

Results

**Figure 1: All patient characteristics**

<table>
<thead>
<tr>
<th>Key:</th>
<th>CTX at baseline</th>
<th>CTX at 4months</th>
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- N=158
- Total Patients 158

**Figure 2: CTX at 0, 4, 12 months all patients (<0.51 at baseline)**

**Figure 3: CTX at 0, 4, 12 months for defined populations**

- a) < pre-menopausal mean at baseline
- b) > pre-menopausal mean at baseline

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

- At Baseline
  - CTX ≤ pre-menopausal mean* (68%)
- 4 month Review
  - CTX suppressed? (i.e. ≤ mean or LSC not achieved)
  - N
- 12 month Review
  - CTX suppressed? (i.e. ≤ mean or LSC not achieved)
  - N

- Delay restart? (72%)
- Consider restart (28%)
- Delay restart (47%)
- Consider restart (53%)

**References**


**Conclusions**

- 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
- 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

**Conflicts of interest: None declared**