Monitoring osteoporosis treatment with oral bisphosphonates

Background
The decision to introduce osteoporosis treatment is based on fracture risk assessment, often including measurement of bone mineral density (BMD). BMD measurements are strongly predictive of fracture risk and are the basis for diagnosis of osteoporosis. BMD measurements are not, however, a good tool to assess response to most osteoporosis treatments.

Why monitor osteoporosis treatment?
First-line treatment for osteoporosis is usually with oral alendronic acid (70 mg weekly). The aim is for treatment to be taken correctly and regularly for a minimum of 5 years in the first instance and for the patient to remain calcium and vitamin D replete during this time. Treatment needs to be taken according to detailed instructions:

- First thing in the morning
- At least 30 minutes before any food or drink
- Swallowed whole with a large glass of tap water
- The patient must remain upright for at least 30 minutes
- Any calcium-containing supplements must be delayed for 3 hours

Oral bisphosphonates are poorly absorbed with only approximately 1% of each dose being absorbed even with total compliance with these instructions.

Many patients fail to persist with osteoporosis treatment while many others experience a sub-optimal response due to unintentional poor compliance or impaired absorption. Monitoring treatment response identifies poor response enabling treatment to be modified to improve fracture risk reduction. It has also been shown that monitoring treatment response may improve compliance and persistence with osteoporosis treatment.

How is treatment monitored?
It is important to check with the patient that they are following the instructions and continuing to take treatment regularly. Conventionally, osteoporosis treatment has been monitored by making periodic measurements of BMD but this is not an effective method because:

- BMD changes with osteoporosis treatment are small and slow
- The magnitude of measurement error with BMD is similar to the change in response to treatment

In a typical patient it is not possible to measure a significant BMD response until they have taken treatment for over 18 months. In patients with unreliable BMD measurements it may take considerably longer. Serial BMD assessment is not, therefore, a useful technique to improve compliance with treatment as compliance problems generally arise early.
An alternative approach to monitoring is to measure biochemical markers of bone turnover (BTM). These show large and rapid changes in response to osteoporosis treatment allowing detection of a significant treatment response within a few months. It has also been shown that changes in BTM are a better predictor of reduced fracture risk than changes in BMD.

BTM have been used in Sheffield to monitor osteoporosis treatment in the metabolic bone clinics for over 10 years. Until recently, the test involved collection of 3 consecutive morning, second-void urine samples and was not practical for use in primary care. The introduction of a new assay (PINP) gives the opportunity to use biochemical monitoring in the community.

What is PINP?
The N-terminal propeptide of type I collagen (PINP) is a by-product of type I collagen formation released during bone formation. It can be measured in serum and is a good marker to use in clinical practice because it may be measured in a blood sample taken at any time of day and no special precautions are needed over how the sample is collected or transported to the lab.

Although PINP is a marker of bone formation it may be used to monitor treatment with alendronic acid and other treatments which have an anti-resorptive mechanism of action. This is because the processes of bone resorption and formation are closely linked. Within a few months of starting treatment it is usually possible to measure a significant reduction in PINP indicating treatment response.

How is treatment response defined?
The aim of treatment is to reduce bone turnover to a level associated with a low risk of fracture. This can be defined as one or both of the following

- A reduction by more than 10 ng/mL from baseline
- A post-treatment level of below 35 ng/mL (this is the level seen in young adults after bone maturation is complete)

Is there any point in giving treatment if the baseline level of PINP is low?
In a patient with osteoporosis the bone turnover may not be high but there may still be imbalance between the processes of resorption and formation leading to bone loss. It is therefore still helpful to initiate treatment with an anti-resorptive treatment such as alendronic acid to restore bone remodelling balance as treatment has been shown to reduce fracture risk regardless of the baseline level of bone turnover.

What is the significance of a very high level of PINP?
A very high PINP result indicates high bone turnover. This is usually associated with accelerated bone loss and may be an indication that there is an underlying cause of bone loss. Possible causes include vitamin D deficiency and diseases causing osteoporosis (e.g. malabsorption, thyrotoxicosis) or, less commonly, the presence of other pathology (e.g. bone metastases or myeloma).

Importantly, PINP increases following a fracture or orthopaedic surgery with the magnitude of the increase reflecting the size of the bone involved. The increase is maximal after 2-3 months and returns to baseline levels within 12 months. This is why it is important to check whether the patient has sustained a recent fracture, particularly once treatment has commenced.
High PINP may be due to inability of the body to metabolise PINP due to significant hepatic disease. In this situation, other BTM may be more appropriate to monitor treatment and management should be discussed with MBC.

**What should be done if the 6 month measurement of PINP does not show a response to treatment?**

1. **Check compliance with treatment**
   - Both the bisphosphonate and any calcium and vitamin D supplements
   - Ensure the dosing instructions are being followed correctly
     - If poor compliance is identified, re-educate, recheck compliance after 1-2 months and recheck PINP at 6 months
     - If compliance issues cannot be reliably addressed or are due to side effects consider change in treatment
       - If side-effects, consider weekly risedronate, raloxifene, or strontium ranelate
       - If difficulty with oral dosing, consider parenteral preparation such as an annual infusion of zoledronic acid or 6-monthly denosumab

2. **Check whether the patient has sustained any fractures since the baseline measurement**
   - If so, ensure compliance is good and re-check PINP at 6 months

3. **If compliance is good and no fractures, undertake investigations to identify potential malabsorption or other underlying cause of poor response**
   - Bone profile, PTH, Vitamin D, TSH, coeliac antibodies, myeloma screen may be helpful
   - Treat any reversible cause identified
     - Discuss with MBC or refer if appropriate