Bisphosphonate length of treatment in osteoporosis: Guidance on treatment break


- The guidance recommends evaluating the continued need for a bisphosphonate at 5 years, based on an individual's assessment of risk of fracture, but also the balance of risk:benefit of continued bisphosphonate treatment. (3 years for IV zoledronate)
  - Patients at high risk of osteoporotic fracture should continue therapy with a bisphosphonate if no contraindications or intolerance for a further 5 years.
  - Medium risk patients require assessment of BMD for consideration of a treatment break (“drug holiday”) of 2 years for oral bisphosphonates.
  - Low risk patients can stop treatment on completion of 5 years (3 years for IV zoledronate). They however require re-assessment using FRAX and DXA if they suffer a further fracture or their risk factors alter. The FRAX tool can be found here.

- Examples of high risk patients are:
  - Patients age ≥75 in the context of frailty or frequent falls.
  - Post treatment T-score ≤ -2.5 at the femoral neck or total hip.
  - History of hip/vertebral fracture or multiple other fragility fractures.
  - Continuing oral glucocorticoid therapy of ≥7.5mg/day prednisolone or equivalent.
  - Those who sustain low-trauma fracture(s) during treatment: exclude poor adherence to treatment and causes of secondary osteoporosis. Refer for specialist opinion if new fracture sustained after 2 years of bisphosphonate).

- Examples of medium risk patients are:
  - Treatment commenced for a fragility fracture (other than hip or vertebral) over age 75 years without a DXA or BMD consistent with osteopenia on DXA.
  - Treatment commenced for osteoporosis by BMD (T-score ≤ -2.5).

- Examples of low risk patients are those that commenced bisphosphonate treatment;
  - For an indication not consistent with local guidelines.
  - For osteopenia (or no DXA) and risk factors that are no longer relevant.
  - For osteopenia with no fragility fracture or fragility fracture (excluding hip and vertebral) in patient <75 years old.

- Ensure adequate intake of calcium and vitamin D in all patients including those who discontinue bisphosphonates

- The situation with patients after a very long duration of treatment (e.g. > 10 years) is less clear. It may still be appropriate for 'high risk' patients to continue without a treatment break, but the definition of high risk for these purposes should probably be more limited. The situation should be judged on a case by case basis with specialist advice/ support, and the current uncertainties of risk versus benefit discussed with patients where appropriate. Local opinion suggests that the majority of patients deemed 'high risk' after 10 years of treatment would benefit from a treatment break of 2 years.
Treatment algorithm

- Treat with oral bisphosphonate for 5 years in line with local guidance
  - (3 years for intravenous zoledronate)
  - 1st line: alendronate
  - Alternative option risedronate if alendronate is not tolerated or contra-indicated

Check adherence at 3-4 months

If no fracture on treatment assess at 5 years:

Is the patient ‘High risk’?
- Continuing high risk patients (age ≥75 with frailty, frequent falls)
- History of hip/vertebral/ or multiple fragility fractures.
- Continuing oral glucocorticoid therapy of ≥7.5mg/day prednisolone or equivalent
- Post treatment T-score ≤ -2.5 at the femoral neck or total hip.

YES

Is the patient ‘Medium risk’?
- Treatment commenced for a fragility fracture over age 75 years without a DXA or with osteopenia
- Treatment commenced for osteoporosis by BMD (T-score ≤ -2.5)

YES

Assess with DXA:
- Does the patient re-classify as ‘High risk’? i.e. Post treatment T-score ≤ -2.5 at the femoral neck or total hip

YES

Low risk
Stop bisphosphonate therapy
Ensure adequate intake of calcium and vitamin D.
Assess fracture risk in the future as per treatment naïve patients.
Re-assessment using FRAX +/- DXA if they suffer a further fracture or their risk factors alter.

NO

NO

Consider a bisphosphonate treatment break
Ensure adequate intake of calcium and vitamin D
- 2-year break if patient was taking oral bisphosphonate
- 3-year break if patient was treated with zoledronate, but guided by specialist outpatients
- Assess to restart therapy on completion of the break using FRAX in conjunction with a monitoring DXA. Restart if NOGG intervention threshold reached and no contraindication**

Reassess:
- After a new fracture regardless of when this occurs
- If the risk factors alter/ additional risk factors
- If no new fracture occurs, after five further years of therapy (or a further 2 years if treatment break extended)

For patients who fracture whilst on treatment:
- ASSESS ADHERENCE TO THERAPY and exclude causes of secondary osteoporosis.
- If patient sustains a fragility fracture during the first 2 years of bisphosphonate therapy- consider as high risk
- If patient has sustained fragility fracture beyond 2 years of bisphosphonate therapy (or multiple fragility fractures), refer for a DEXA and specialist opinion.

*Risks of prolonged therapy:
- ONJ- patient must always inform dentist of therapy
- AFF- patient must report any thigh, hip or groin pain and this should be evaluated

**Contraindications:
- GFR< 35mL/min
- Swallowing difficulties
- Unable to sit upright
- Severe dyspepsia
Recommendations

- There is good evidence to show that bisphosphonates, such as alendronate, risedronate and zoledronate, reduce the risk of non-vertebral and vertebral fractures in women with osteoporosis. However, there is uncertainty about the optimal duration of therapy, as well as documented rare but serious adverse effects such as osteonecrosis of the jaw and external auditory canal and atypical femoral fractures, that increase in risk the longer normal bone remodelling is suppressed.

- Decisions to stop or continue bisphosphonate treatment after 5 years (3 years for zoledronate) should be based on individual assessment of risks and benefits, following an informed discussion between the clinician and the individual patient.

- Patients at continued high risk of an osteoporotic fracture should continue therapy with a bisphosphonate for a further 5 years, after checking for contra-indications or intolerance, up to which there is clinical trial data of efficacy. However, if post-treatment DXA shows significant BMD loss despite adherence to treatment, refer to specialist outpatients to consider escalation of treatment.

- Patients considered medium risk require assessment of BMD for consideration of a treatment break (“drug holiday”) of 2 years or to reclassify as high risk (post treatment T-score ≤ -2.5 at the femoral neck or total hip). Practitioners should be aware that fracture risk calculators such as FRAX or Qfracture are only validated in treatment naïve patients, and the use to reassess treated patients should be undertaken with caution.

- Low risk patients can stop bisphosphonate treatment without a repeat DXA. Their fracture risk should then be assessed in the future as per treatment naïve patients.

- A treatment break should be viewed as a temporary, not permanent, suspension of active therapy. It should be remembered that discontinuing a bisphosphonate can safely be performed due to the persistence of the antiresorptive and anti-fracture effect expected for an undefined period of time (Approximately 1-2 years with risedronate, 2-3 years with alendronate and 2-3 years or more with zoledronate.)

- For patients on a treatment break from oral bisphosphonates, recommencing therapy should be assessed after 2 years, or sooner if additional risk factors become relevant or a new fragility fracture occurs. If fracture risk by DXA and a screening tool (FRAX) reaches the NOGG intervention threshold, then restart therapy after checking for contraindications, and discussing with the patient that the risk of side-effects has been reduced by the treatment break. If it does not reach threshold, reassess in a further 2 years. If the patient is greater than 90 years old within the “Medium Risk” cohort recommence therapy after 2 years without reassessment of fracture risk (FRAX under-estimates fracture risk in the elderly due to confounding mortality statistics).

- The treatment break for patients on zoledronate will be managed by specialist outpatients often with monitoring of bone turnover markers to determine duration (approximately 3 years).

- It is important to ensure patients have adequate levels of dietary calcium and vitamin D during treatment break or on discontinuation of treatment. See osteoporosis guidance for recommendation on supplementation.

- If treatment is discontinued fracture risk should be reassessed:
  - After a new fracture regardless of when this occurs.
  - If the patient is found to have additional risk factors for fracture.
  - If no new fracture or risk factors occur, after five years (or 2 years in the context of a treatment break).

Fracture risk assessment will determine whether a patient restarts treatment. FRAX is a useful screening tool to identify appropriate patients that are at risk of primary osteoporosis. FRAX tool can be found here.
Patients taking long term bisphosphonates should be advised to report any thigh, hip or groin pain which may be indicative of an atypical femoral femur. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered while they are evaluated. Patients who develop atypical femur fractures whilst on treatment for osteoporosis will inevitably require a review of treatment from the osteoporosis team.

References
1. NOGG Clinical Guideline March 2017, updated July 2018
   https://www.sheffield.ac.uk/NOGG/NOGG%20Guideline%202017.pdf Derbyshire preferred choice formulary
2. QIPP detail aid. Bisphosphonates – is a holiday necessary? July 2013
5. MHRA Drug Safety Update Dec 2015 Vol 9, issue 5
7. Fracture Reduction in South Central policy group, Anti-osteoporosis Medication duration of therapy Review 2016
8. Royal Osteoporosis Society Duration of Osteoporosis Treatment June 2018
   https://theros.org.uk/media/100519/duration-of-osteoporosis-treatment-flowchart.pdf

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<td>Flow chart updated- risk assess with FRAX after completion of treatment break</td>
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<td>p.1 <code>specialist outpatients</code> replaced with specialist advice/ support</td>
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