North Central London
Joint Formulary Committee

Bisphosphonate Treatment Duration in Women Position Statement

Bisphosphonates are routinely used as a treatment for osteoporosis. Alendronic acid is the most commonly prescribed bisphosphonate in NCL. Optimal duration of bisphosphonate treatment is important to balance the risks and benefits of these medicines.

Alendronic acid, risedronate and ibandronic acid should be reviewed after 5 years of treatment. Zoledronic acid should be reviewed after 3 years of treatment. Patients with no new fracture and femoral BMD T-score > -2.5 can generally have treatment withdrawn. Certain groups of higher risk individuals (see points 11, 12 and 13 below) should generally continue bisphosphonate treatment without need for a treatment break.

Following withdrawal of treatment, re-evaluate fracture risk (using FRAX® and femoral neck BMD) and consider restarting treatment after 2 years (alendronate, risedronate, ibandronate) or 3 years (zoledronic acid).

Fracture risk should be re-evaluated if a new fracture occurs. Further treatment can be with the same bisphosphonate used previously.

These recommendations apply only to women.

1. The risk of osteonecrosis of the jaw and atypical femoral fractures whilst on bisphosphonate treatment has led to questions about the optimal treatment duration for bisphosphonates. [1]
2. There is insufficient evidence to guide optimal treatment durations in men, therefore these recommendations apply only in women. [1]
3. Bisphosphonates are commonly prescribed medicines for the primary and secondary prevention of fragility fractures in women with osteoporosis. [2] [3] Use of bisphosphonates is supported by NICE Technology Appraisals for both primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women. [2] [3] The most commonly prescribed bisphosphonate in primary care in NCL is alendronic acid (89% items), followed by risedronate (7% items).
4. Bisphosphonates bind to bone mineral to inhibit bone turnover. The terminal half-life of bisphosphonates can exceed ten years as it is released from bone. [4] This long half-life has led to the concern about the impact of long-term treatment on bone remodelling. [5]
5. Osteoporosis is classified as a bone mineral density (BMD) of at least 2.5 standard deviations below the mean value for a young adult woman (i.e. T-score ≤ - 2.5 SD). [1] 'Severe' or 'established' osteoporosis has been used to describe osteoporosis that meets the above T-score threshold in addition to presence of at least one fragility fracture. [1]
6. Risk of fracture should be presented as a 10 year risk, to cover the period of treatment and the period during which post-treatment benefits may continue. The FRAX® tool is externally validated to provide age-related fracture probability based on assessment of BMD, age and independent risk factors. For each age group, NOGG has provided an **Intervention threshold**, above which treatment should be considered. [1] These can be used for starting treatment and resuming treatment following a break.
7. NICE Guideline 56 (Multimorbidity: clinical assessment and management) advises that there is no consistent evidence of further benefit from continuing bisphosphonates for another 3 years following treatment for at least 3 years. They also acknowledge that there is no consistent evidence of harm from stopping bisphosphonate after 3 years of treatment. [6]
    - This recommendation was reached following evaluation of five RCTs assessing risks and benefits of discontinuing bisphosphonate treatment. No other drugs for osteoporosis were evaluated in these studies. Both primary and secondary fracture prevention patients were included.
8. MHRA has advised that bisphosphonate treatment has been rarely associated with atypical femoral fractures. This is mainly in patients receiving long-term treatment. Continued treatment should be re-evaluated periodically, particularly after 5 or more years of use. [7]
9. The National Osteoporosis Guideline Group (NOGG) has proposed that alendronic acid, risedronate and ibandronate should be reviewed after five years of treatment; zoledronic acid should be reviewed after three years. [1]
    - The key evidence for discontinuation of alendronic acid was Black *et al* (2006) which included patients with a mean treatment duration of 5 years [8]

- Zoledronic acid should be reviewed after 3 years of treatment based on the evidence from Black *et al* (2012) [9]

10. Patients with no new fracture and femoral BMD T-score > -2.5 can generally have treatment withdrawn unless they meet on of the criteria described below.
11. Certain groups of individuals can generally continue treatment (beyond 5 years for oral bisphosphonates or 3 years for IV) without further assessment, though review after six years (IV therapy) to ten years (oral therapy) is recommended: [1]
    - Age ≥ 75 years
    - Previous hip or vertebral fracture
    - Low trauma fracture during treatment (with good adherence) and following exclusion of secondary osteoporosis *
    - Femoral neck BMD T-score ≤ -2.5 SD
12. Osteoporosis and fractures are a common side effect of aromatase inhibitors (e.g. letrozole). [10] Extended use of aromatase inhibitors (> 5 years) may require additional long-term use of bisphosphonate
13. Bisphosphonate treatment will usually be continued without a treatment break for patients taking more than 7.5 mg prednisolone or equivalent daily. FRAX® is likely to underestimate fracture risk in these patients. [1]
14. People with glucocorticoid induced osteoporosis receiving low dose continuous oral glucocorticoid (equivalent to ≤ 7.5 mg prednisolone daily) should have their bisphosphonate reviewed regularly in the same way as other patients. [1]
15. Following withdrawal of treatment in any patient, re-evaluate fracture risk and consider restarting treatment after 2 years (alendronate, risedronate, ibandronate) or 3 years (zoledronic acid). FRAX® and femoral neck BMD can be used to calculate fracture risk. If femoral neck BMD T-score is ≤ -2.5, consider resuming treatment regardless of FRAX® fracture probability. [1] BMD decreases and increased bone turnover can be seen 2 to 3 years (alendronate) or 1 to 2 years (risedronate / ibandronic acid) after withdrawing bisphosphonate treatment.
16. NOGG advises that there is no evidence base to guide treatment beyond 10 years; management should be on an individual patient basis [1]
17. A daily intake of calcium (700 mg to 1200 mg) is recommended when treatment with bisphosphonate has been discontinued. This should be achieved through diet where possible, with supplementation reserved for patients unable to achieve this intake through diet alone. (See NCL Calcium and Vitamin D guideline for further information)
18. Patients should remain vitamin D replete when treatment with bisphosphonate has been discontinued. (See NCL Calcium and Vitamin D guideline for further information)
19. Estimating skeletal bone turnover from biochemical markers (e.g. PINP, BSAP and beta-CTX) may be useful during the "off-treatment" period. If suggestion of relapse from suppressed bone turnover and BMD has decreased, consider resuming treatment [1]
20. Dual energy X-ray absorptiometry (DXA) of femoral neck is the preferred site for evaluating fracture risk, particularly in elderly patients. [1] Spine is not favoured for diagnosis (particularly in the elderly) because of prevalence of arthrosis and arthritis. DXA of the spine is preferred for assessing response to bisphosphonate treatment. [1]

* NICE TA 161 recommends teriparatide as an option for secondary prevention of osteoporotic fragility fractures in post-menopausal women who have had a further fragility fracture despite fully adhering to treatment for one year and where there is evidence of a decline in BMD below her pre-treatment baseline. [2]

References

[1] National Osteoporosis Guideline Group, "Clinical guideline for the prevention and treatment of osteoporosis," March 2017.

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[4] Aurobindo Pharma - Milpharm Ltd., *Summary of product characteristics. Alendronic acid 70mg tablets.,* Updated: Sept 2015.

[5] PrescQIPP, *Bisphosphonate treatment break,* December 2015.

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Groups / Individuals who have overseen the development of this guidance:	JFC Support Pharmacists, Dr Lee (RFL), Dr Keen (UCLH/RNOH), Nisha Patel (Camden CCG)
Groups which were consulted and have given approval:	Acute Trusts and CCGs in NCL
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