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PrescQIPP Community Interest Company

Bisphosphonate treatment break

Bisphosphonates have been widely used in the treatment of osteoporosis with robust data demonstrating efficacy in fracture risk reduction over three to five years of treatment. They bind strongly to bone mineral and inhibit bone turnover and this effect lasts for many months after treatment has stopped. This has led to the concern that long term treatment may increase bone fragility by suppressing normal bone remodelling, essential for repair of skeletal micro-damage.

There is some debate over the ideal duration of therapy, particularly with the emergence of links with the rare but serious complications of osteonecrosis of the jaw and atypical subtrochanteric fracture.

As these agents accumulate in bone with some persistent anti-fracture efficacy after therapy is stopped, it is reasonable to consider a treatment break (drug holiday).

Annually £11.2 million (ePACT April to June 2015) is spent in England on prescribing bisphosphonates for the treatment and prophylaxis of osteoporosis and £268,000 on non-osteoporosis conditions (Paget's disease and bone metastases in breast cancer).

This bulletin recommends review of prescribing and consideration of a treatment break for patients who have been on oral bisphosphonates for five years for osteoporosis.

Bisphosphonate prescribing for all patients should be reviewed to consider the most appropriate, cost effective preparation is being prescribed.

Supporting data and a patient information leaflet are also available: http://www.prescqipp.info/resources/viewcategory/401-osteoporosis-bisphosphonate-treatment-breaks

Recommendations

- Review indication for all patients prescribed bisphosphonates.
- Ensure product and dose prescribed are appropriate for indication.
- Re-assess patients at high risk of osteoporotic fracture at regular intervals and at least every five years.
- Consider stopping therapy (a treatment break) for patients who have been on bisphosphonates for three to five years if at moderate risk of osteoporotic fracture.
- Consider discontinuation of therapy for low risk patients.
- Review cost effectiveness of preparations prescribed.

Rationale

Bisphosphonates have a well-established place in the treatment of osteoporosis.

They bind strongly to bone mineral and inhibit bone turnover, remaining within the bone with a half-life of at least ten years.[1] This has led to the concern that long term treatment may increase bone fragility by suppressing normal bone remodelling, essential for repair of skeletal micro-damage. Links have emerged with the rare but serious complications of osteonecrosis of the jaw and atypical subtrochanteric fracture.

The Medicines and Healthcare Products Regulatory Agency (MHRA) has warned of the risk of atypical femoral fractures with long term bisphosphonate use.[2] The British National Formulary (BNF) quotes advice from the MHRA for the need to re-evaluate prescribing periodically and particularly after five years.[3] The Summary of Product Characteristics (SPCs) for oral bisphosphonates contain advice that duration of treatment should be reviewed periodically and the benefit and potential risk should be re-evaluated for each patient particularly after five years of use.[4-6]

Follow up should be arranged to assess the following:

- Adverse effects of treatment
- Adherence to treatment
- Need for continuing treatment with biphosphonates.

Guidance on drug holidays has been produced by The National Osteoporosis Guideline Group (NOGG) and the Canadian Menopause and Osteoporosis working group.[7,8] Further evidence is provided by the American Food and Drug Administration (FDA) which has suggested guidance after having considered two trials.[9] There is agreement on the need for treatment reviews at regular intervals and drug holidays for patients at moderate risk of fracture to reduce the risk of long term harmful effects.

The FDA considered the FLEX and HORIZON extension trials which have shown that bone loss after discontinuation of therapy was modest compared with continued therapy.[10,11] The results of FLEX and HORIZON extension studies suggest that patients with bone mineral density (BMD) measured as femoral neck T score greater than -2.5 after three to five years of treatment and who did not suffer further fragility fractures, are unlikely to benefit from continued treatment.

In patients receiving oral bisphosphonates (alendronate, ibandronate, risedronate and etidronate), treatment is usually given for five years in the first instance. If BMD remains the same or has improved from baseline, the post-treatment femoral neck T-score is greater than −2.5 and no fractures have occurred during treatment, it is advisable to discuss a bisphosphonate treatment break (drug holiday) for two to three years, with reassessment of fracture risk at the end of that time and re-continuation of treatment if indicated.

The FDA has suggested that patients at high risk should continue therapy. During treatment patients should be encouraged to report any thigh, hip or groin pain which may be indicative of an atypical femoral fracture. http://www.fda.gov/Drugs/DrugSafety/ucm263320.htm

NOGG suggests continuation of treatment can generally be recommended in the following groups of high risk individuals:[7]

- Those aged 75 years or more
- Those who have previously sustained a hip or vertebral fracture
- Those who are taking continuous oral glucocorticoids in a dose of ≥ 7.5 mg/day prednisolone or equivalent.
- Individuals who sustain one or more low trauma fractures during treatment, after exclusion of poor adherence to treatment, (for example less than 80% of treatment has been taken) and after causes of secondary osteoporosis have been excluded. In such cases the treatment option should be re-evaluated.

Patients with low bone mineral density at the femoral neck (T score below −2.5) after three to five years of treatment are at the highest risk for vertebral fractures and therefore appear to benefit most from continuation of bisphosphonates.[9]

Patients with an existing vertebral fracture, who have a T score less than -2, may also benefit from continued therapy.

Following informed discussion, a drug holiday can be considered in patients who are not at high risk or those whose femoral neck T score is greater than −2.5, Consider discontinuing bisphosphonates after three to five years.[9]

The duration of treatment and the length of the 'holiday' should be tailored to individual patient circumstances and based on individual assessments of risk and benefit. In clinical practice, monitoring BMD and bone turnover marker (BTM) are the only means of gaining some sense of the loss of the effect of the bisphosphonate on bone remodeling, but ultimately the duration of the holiday should be based on clinical judgment.[9]

Patients with a femoral neck T score above −2.0 have a low risk of vertebral fracture and are unlikely to benefit from continued treatment. These patients should discontinue therapy, restarting when and if indications for therapy are met.[9]

Further guidance on measuring risk is available from NICE and from tools such as FRAX® and QFracture®.[12-14]

Watts and Diab considered scenarios for length of treatment and of drug holiday.[15] These are shown in table 1 and illustrate the guidance.

Table 1: Length of treatment with bisphosphonates including scenarios[15]

Risk	Example	Treatment guidelines
Low risk of fracture	53-year-old woman, menopause at age 50 years, lowest T-score −1.6, no risk factors, bisphosphonate therapy for 2 years. Treatment was not indicated in the first place and can be discontinued.	Treatment not necessary. If bisphosphonate has been prescribed, it should be discontinued and not restarted until patient meets treatment guidelines.
Mild risk of fracture	65-year old woman, menopause at age 52 years, lowest initial T-score −2.6, no risk factors, bisphosphonate treatment for 5 years, BMD stable over that time. Treatment was indicated, but after 5 years of treatment, a drug holiday might be considered.	Treat with bisphosphonate for 3–5 years, then stop. The 'drug holiday' can be continued until there is significant loss of BMD (i.e. more than the least significant change as determined by the testing centre) or the patient has a fracture, whichever comes first.
Moderate risk of fracture	70-year-old woman, menopause at age 49 years, lowest initial T-score −2.7, no risk factors, bisphosphonate therapy for 8 years, BMD increased over that time so lowest T-score now is −2.3. Treatment was indicated, but after 8 years of treatment, a drug holiday might be considered.	Treat with bisphosphonate for 5–10 years, offer a 'drug holiday' of 3–5 years or until there is significant loss of BMD or the patient has a fracture, whichever comes first.
High risk of fracture (fractures, corticosteroid therapy, very low BMD)	72-year-old woman, menopause at age 43 years, lowest initial T-score −3.8, rheumatoid arthritis requiring ongoing corticosteroid therapy for 12 years, 3-inch height loss and two vertebral fractures by Vertebral Fracture Assessment (VFA), treatment with bisphosphonate therapy for 10 years. Treatment was indicated. After 10 years she remains at high risk of fracture. If a holiday from the bisphosphonate is considered, interval treatment with teriparatide or raloxifene would be prudent.	Treat with bisphosphonate for 10 years, offer a 'drug holiday' of 1–2 years, until there is significant loss of BMD or the patient has a fracture, whichever comes first.

As the different drugs have varied skeletal affinity, if a drug holiday is advised, reassessment of risk should occur sooner for drugs with lower skeletal affinity, with a suggestion to reassess after:[16]

- 1 year for risedronate
- 1-2 years for Ibandronate
- 1–2 years for alendronate
- 2–3 years for zoledronic acid.

NOTE: This does not apply to patients who continue to take oral steroids, since they continue to have an increased fracture risk. Such patients should be excluded from this review.

The effects of other anti-resorptive treatments (denosumab, raloxifene, strontium ranelate, teriparatide) wear off more rapidly when treatment is stopped and there is no clear case for drug holidays in patients receiving these drugs.

Costs

The cost of different products should be considered where treatment is to be continued.

Table 2: Costs of bisphosphonate products

Product	28 day cost of branded BNF[2]	28 day cost of generic or individual components drug tariff[17]
Alendronic acid	Fosamax once weekly tablets 70mg £22.80[4]	£0.96[4]
Ibandronic acid	Bonviva tablets 150mg £18.40[1]	£1.61[1]
Risedronate sodium	Actonel once a week tablets 35mg £19.12[4]	£1.19[4]

Costs of individual products as per BNF July 2015 and Drug Tariff August 2015 are shown in table 2.[3,17] The lowest cost product or combination should always be supplied unless there is a clinical reason not to do so.

Total savings available nationally, assuming a one year drug holiday every five years, are almost £1.8 million annually (ePACT April to July). This equates to £3,146 per 100,000 patients. Savings would be higher for longer treatment breaks and lower if patients that do not need a treatment break are excluded. Savings from avoided hospital admissions and patient benefit have not been identified in this bulletin but are nevertheless available.

The attached data pack shows prescribing data at CCG level and annual savings available for each CCG

Summary

- Audit indication for all patients prescribed bisphosphonates.
- Re-assess patients at high risk at regular intervals and at least every five years.
- Consider stopping therapy (a drug holiday) for patients who have been on bisphosphonates for three to five years if at moderate risk of osteoporotic fracture.
- Consider discontinuation of therapy for low risk patients.
- Review cost effectiveness of all bisphosphonate preparations.

Further reading

BMJ state of the art review: Bisphosphonates for the prevention and treatment of osteoporosis. BMJ 2015;351:h3783. Available at http://www.bmj.com/content/bmj/351/bmj.h3783.full.pdf

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Additional PrescQIPP resources

 Data pack

 Patient information

Available here: http://www.prescqipp.info/resources/viewcategory/401-osteoporosis-bisphosphonate-treatment-breaks

Information compiled by Dipti Patel, PrescQIPP Programme, October 2015 and reviewed by Katie Taylor, Senior Medicines Evidence Reviewer, PrescQIPP Programme, November 2015.

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