Bisphosphonates: Duration of Treatment and Drug Holidays

Background information

Drug holidays are only ever possible with bisphosphonates. This is because bisphosphonates are retained long term in bone allowing the beneficial effects to persist for some time after cessation of treatment administration. The bone retention varies with zoledronic acid > alendronate > risedronate.

Two RCTs have been conducted:

- FLEX[1]: 5 years vs 10 years of alendronate. In the final 5 years of that study:
  - No significant difference in hip or nonvertebral fractures.
  - Significantly greater clinical vertebral fractures for those offered the 5-year drug holiday.
- HORIZON study extension[2]: 3 years vs 6 years of yearly zoledronic acid. In the final 3 years of that study:
  - No significant difference in hip or nonvertebral fractures.
  - Significantly greater morphometric vertebral fractures (radiologic rather than clinical) in those offered the 3-year drug holiday.

Two organizations have developed Clinical Practice Guidelines for osteoporosis using GRADE methodology: UK National Osteoporosis Guideline Group (NOGG)[3] published in September 2021 and Osteoporosis Canada (OC) CPGs published in October 2023.[4] In my own practice, on the very specific issue of duration of treatment and drug holiday, I usually follow the NOGG CPGs because of their clear and detailed guidance and their close alignment with the evidence. For your convenience I offer the most relevant excerpts from both CPGs.

<u>Please note that both CPGs recommend resumption of osteoporosis therapy for any patients who experience a fragility fracture during a drug holiday.</u>

Excerpts from OC's CPGs[4]:

- For people on bisphosphonates, we suggest initial therapy for a duration of 3-6 years. Remark: Six year of therapy is appropriate for individuals with a history of hip, vertebral or multiple nonvertebral fractures, or new or ongoing risk factor(s) for accelerated bone loss or fracture.‡ When using zoledronic acid, dosing less frequently than annually may be appropriate.

  Conditional recommendation; low certainty evidence

- Three years after stopping bisphosphonate therapy (i.e., drug holiday), we suggest repeating BMD measurement and clinical reassessment of fracture risk to determine the need for resumption of therapy. We suggest following the recommendations for risk assessment and initiation of pharmacotherapy. Remark: A shorter interval for reassessment to resume therapy may be appropriate in people with higher risk of fracture (such as previous hip fracture or high FRAX or CAROC score), secondary causes of osteoporosis, new fracture or new clinical risk factors associated with rapid bone loss. ‡

  Conditional recommendation; very low-certainty evidence.

‡See risk factors in Figure 1 and Appendix 1, Supplementary Table 5 (causes of secondary osteoporosis), available at www.cmaj.ca/lookup/doi/10.10503/cmaj.221647/tab-related-content

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Excerpts from the UK's NOGG CPGs[3] – please note that ibandronate is not available in Canada and that prednisone and prednisolone dosages are equivalent**:**

1. Plan to prescribe oral bisphosphonates (alendronate, ibandronate and risedronate) for at least 5 years and then re-assess fracture risk. Longer durations of treatment, for at least 10 years, are recommended in the following men and women (Strong recommendation):

- Age ≥70 years at the time that the bisphosphonate is started
- Who have a previous history of a hip or vertebral fracture(s)
- Treated with oral glucocorticoids ≥7.5 mg prednisolone*/day or equivalent
- Who experience one or more fragility fractures during the first 5 years of treatment (if treatment is not changed).

2. Plan to prescribe intravenous bisphosphonate (i.e., zoledronate) for at least 3 years and then re-assess fracture risk. Longer durations of treatment, for at least 6 years, are recommended in the following men and women (Strong recommendation):

- Age ≥70 years at the time that the bisphosphonate is started
- Who have a previous history of a hip or vertebral fracture(s)
- Treated with oral glucocorticoids ≥7.5 mg prednisolone*/day or equivalent
- Who experience one or more fragility fractures during the first 3 years of treatment (if treatment is not changed).

3. If a new fracture occurs after bisphosphonate treatment is discontinued, reassess using FRAX and restart treatment (Strong recommendation).

4. If bisphosphonate treatment is discontinued and no new fracture occurs, reassess using FRAX after 18 months for risedronate and ibandronate, 2 years for alendronate, and 3 years for zoledronate to inform whether treatment should be restarted (Strong recommendation).

5. After 10 years of bisphosphonate treatment, patient management should be considered on an individual basis (Conditional recommendation).

My advice:

1. Only offer osteoporosis treatment to those who need it, typically if fracture risk is ≥ 20% or if fragility fracture of hip or spine or two or more major osteoporotic fractures after 50. If they don't need it, stop it. This is not a drug holiday. Reassess fracture risk in 3 years if patient's 10-yr risk of fracture is 15-19.9%, in 5 years for fracture risk of 10-14.9% or 10 years for fracture risk < 10%.
2. If patient does need osteoporosis treatment, then follow the NOGG CPG advice as above.
3. For patients where it's not quite as clear if they should be offered treatment or not (e.g., major osteoporotic fragility fracture patient with a more borderline 10-yr fracture risk of 15-19.9%), then a shorter course of treatment would be preferable. I would recommend 3 years of an oral bisphosphonate or 1 single dose of zoledronic acid.

References

1. Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. Jama 2006; 296(24): 2927-38.
2. Black DM, Reid IR, Boonen S, et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Mineral Research 2012; 27(2): 243-54.
3. NOGG 2021: Clinical guideline for the prevention and treatment of osteoporosis, September 2021. Accessed online on Dec 4, 2023 at: Full Guideline | NOGG
4. Morin SN, Feldman S, Funnell L, et al. Clinical practice guideline for the management of osteoporosis and fracture prevention in Canada: 2023 update. CMAJ 2023 October 10;195:E1333-48.

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