Bisphosphonates: forever or 5 years and stop?

Michael R. Kolber MD  CCP  MSc  Cheryl A. Sadowski PharmD  FCSHP
Christina Korownyk MD  CCP

Clinical question
Does fracture risk increase if patients with osteoporosis discontinue bisphosphonates after 5 years?

Bottom line
Available evidence suggests that after 5 years of treatment, discontinuation of bisphosphonates does not increase fracture risk. If certain subgroups should continue therapy beyond 5 years and when or if therapy should be reinitiated remains uncertain.

Evidence
• FLEX1: An RCT of 1099 postmenopausal women with osteoporosis (mean age 73, 60% with previous fracture, 4- to 5-year use of alendronate) randomized to 5 mg or 10 mg of alendronate or placebo. After 5 additional years, bone mineral density (BMD) scores in the placebo group were lower than in the alendronate group, and total nonvertebral fractures and total vertebral fractures were not statistically different. In the total clinical vertebral fracture subgroup, alendronate statistically significantly lowered fractures (2.4% vs 5.3% with placebo). Number needed to treat is 36 for continuing alendronate.
-Although patients with lower BMD or previous fracture had a higher risk of fractures, there was no statistically significant benefit seen in these subgroups.
• HORIZON-PFT2: An RCT of 1233 patients randomized to stop or continue zoledronic acid for 3 years (after 3 years of therapy) also found no difference in clinical fractures.

Context
• Two smaller, flawed studies examining discontinuation of bisphosphonates (without randomization) also found those discontinuing therapy had lower BMD,3,4 residual fracture protection,5 and no statistical difference in fracture rates versus those continuing therapy.5
• Interpreting osteoporosis studies is challenging: there is considerable heterogeneity among populations studied, how BMD is reported, and fracture classifications; there is large variability in BMD scores; and evaluation of symptomatic fractures (the clinically most important outcome) is not always included in study designs.
• Observational studies demonstrate potential adverse events with bisphosphonates (gastrointestinal, bone).6,7
• No consensus exists regarding optimal duration of bisphosphonate therapy. Some suggest stopping bisphosphonates after 5 years in lower-risk patients (eg, those without previous fractures); however, this subgroup selection is not based on RCT evidence.

Implementation
The relative benefit of bisphosphonates for fracture prevention is about 30% (range 20% to 50%).8,9,10 Therefore, if a patient’s 10-year fracture risk is 10%, bisphosphonates can reduce that risk to about 7%. If a patient’s absolute 10-year fracture risk (with and without treatment) is reported, fewer osteoporosis medications are prescribed without an increase in subsequent fractures.11 In Canada 66% of seniors are taking at least 5 medications per year.12 Patient preferences, including medication reduction, should be considered and surrogate marker–focused outcomes avoided.13 Providing 10-year fracture risk with BMD scores and discontinuing osteoporotic medications after 5 years might help reduce polypharmacy in seniors.

Dr Kolber is Associate Professor in the Department of Family Medicine. Dr Sadowski is Associate Professor in the Faculty of Pharmacy and Pharmaceutical Sciences, and Dr Korownyk is Associate Professor in the Department of Family Medicine, all at the University of Alberta in Edmonton.

The opinions expressed in Tools for Practice articles are those of the authors and do not necessarily mirror the perspective and policy of the Alberta College of Family Physicians.

References