Bisphosphonates: forever or 5 years and stop?

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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

- FLEX[1]: 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-PFT[2]: 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,[4] and no statistical difference in fracture rates versus those continuing therapy.[3]
- 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[5]; 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)[8]; 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%).[6,9,10] 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.

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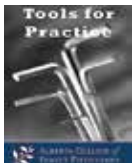

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