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Evidence Updated: None
Bottom Line: Unchanged
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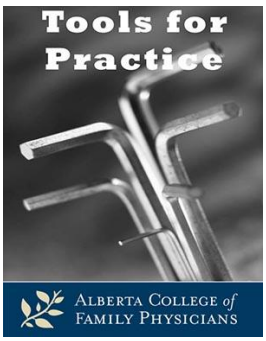

Bisphosphonates: Forever or Five Years and Stop?

Clinical Question: Can patients with osteoporosis who have taken bisphosphonates for five years discontinue treatment without increasing future fracture risk?

Bottom Line: Available evidence suggests that after five years of treatment, discontinuation of bisphosphonates carries little to no increased future fracture risk. Choosing appropriate patients to continue therapy beyond five years and determining when or if to reinitiate therapy in those discontinued, remains uncertain.

Evidence:

- FLEX[1]: Randomized controlled trial (RCT) of 1,099 post-menopausal women with osteoporosis (mean age 73, 60% with previous fracture) previously on alendronate for 4-5 years. Patients were randomized to alendronate 5 mg, 10 mg, or placebo. After five additional years:
  - Bone mineral density (BMD) measurements in the placebo group were lower than the alendronate group.
  - Total non-vertebral fractures and total vertebral fractures were not statistically different.
    - In only one outcome subgroup, total clinical vertebral fractures, alendronate statistically significantly lowered fractures (2.4% versus 5.3% placebo). Number needed to treat is 36 for continuing alendronate.
  - Although patients with lower BMD or previous fractures had a higher risk of fractures, there was no statistically significant benefit seen in these subgroups.
- HORIZON – Pivotal Fracture Trial extension: RCT of 1,233 patients randomized to stopping or continuing zoledronic acid for three years (after three years of therapy) also found no difference in clinical fractures.[2]

Context:

- Two smaller flawed studies examining discontinuation of bisphosphonates (without randomization) also found those discontinuing had: (1) Lower BMDs,[3,4] (2) Residual

fracture protection,[4] and (3) No statistical difference in fracture rates compared to those continuing therapy.[3]

- Interpreting osteoporosis studies presents many challenges:
  - Significant heterogeneity among populations studied, how BMD is reported and the classifications of fractures.
  - Large variability in BMD measurements make interpretation difficult.[5]
  - Many studies are not designed to evaluate symptomatic fractures, the clinically most important outcome.
- Observational studies demonstrate potential adverse events with bisphosphonate (gastrointestinal, bone).[6,7]
- No consensus exists regarding optimal duration of bisphosphonate therapy.
  - Some suggest stopping bisphosphonates after five years in lower risk patients, such as those without previous fractures.[8]
    - This subgroup selection is not based on RCT evidence.

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