Clinical Practice Assessment
Bisphosphonate therapy drug holiday

Clinical Question:
Is there a role for a drug holiday following Bisphosphonate therapy?

Bottom line:
There is no consensus regarding drug holidays in postmenopausal women being treated with bisphosphonates. Patients with the highest risk of osteoporotic fracture appear to have the greatest benefit from continued Bisphosphonate therapy. Risk calculators (e.g. FRAX) can help identify these patients.

Synopsis:
Discontinuation of Alendronate in women with a bone mineral density after 5 years of treatment greater than baseline and T scores greater than -3.5 resulted in (Black et al., 2006 cited in Rosen, 2014):
1. A gradual decline in bone density at the total hip and spine.
2. No significant difference in the incidence of nonvertebral fractures.
3. Increased risk of fractures detected by spine radiographs and the individual’s clinician.
4. No significant increase in risk of morphometrically detectable vertebral fractures (determined by lateral spine radiographs).
There were no differences in the rate of adverse events in the group that continued daily alendronate therapy versus placebo.

Discontinuation after 3 years of annual treatment with 5 mg Zoledronic acid intravenously(Black et al., 2007 cited in Rosen, 2014):
1. Did not result in a higher risk of clinically evident fractures
2. Morphometric fracture rate was lower in the group that received 6 years of Zoledronic acid than the control/placebo group.
The overall rate of fractures was low and determination of morphometric fractures was a secondary end point. One case of osteonecrosis of jaw occurred in the active treatment group. No atypical fractures occurred in either group.

No extension studies with Risedronate are available to determine risks and benefits of a drug holiday.

Atypical fractures are known to occur in non-users of bisphosphonates and there is a higher incidence with increasing age in older women. Cohort studies and secondary analyses of bisphosphonate study data suggest that the risk of atypical femoral fractures is low and the benefit of continued bisphosphonate therapy outweighs the risk of atypical fractures.

In the study of osteoporotic fractures (Napoli et al., 2013) the incidence of atypical femoral fractures was 3.2 per 10,000 person years compared with a total hip fracture incidence of 110 per 10,000 person years. Bisphosphonate use was estimated to
decrease the risk of fracture by 39% in this study. The absolute risk of atypical fractures during 5-6 years of bisphosphonate therapy was 0.13%. In another retrospective analysis of three randomized bisphosphonate trials (two with oral Alendronate and one with intravenous Zoledronic acid infusion annually) the risk of atypical femoral fractures was found to be low (Black et al., 2010). The combined rate of atypical fractures was 2.3 per 10,000 patient years. These trials evaluated patients who were treated with bisphosphonates for up to 10 years.

References:

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