

Bisphosphonate drug holidays: Can we recommend currently?

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ABSTRACT

Bisphosphonates (BP) are the mainstay of treatment for osteoporosis. Subtrochanteric or diaphyseal fractures have been reported with long term use of BP, which raised world-wide debate on two aspects, i.e., for how long the BP is to be given and potential advantages/role of BP drug holidays. BP accumulates in bone with some persistent protective effect after therapy is stopped endorses the concept. Theoretically, a drug holiday may be a considerable option to decrease risks of BP, which continuing the protection from fractures but the level of evidence and data supporting the concept of drug holidays is a week. Hence, no specific recommendations are available on BP drug holidays from major available treatment guidelines on postmenopausal osteoporosis. Hence, before it is recommended it requires more robust research in this field.

Key Words: Bisphosphonates, drug holidays, osteoporosis, postmenopausal

INTRODUCTION

Bisphosphonates (BP) are the mainstay of treatment for postmenopausal osteoporosis worldwide with established efficacy in the prevention of vertebral and nonvertebral fractures.^[1-3]

They are generally well-tolerated and safe. However, there are some adverse drug reactions reported with BP such as gastrointestinal effects, acute phase reactions, musculoskeletal pain, atrial fibrillation, subtrochanteric or diaphyseal fracture, osteonecrosis of the jaw (ONJ), cutaneous hypersensitivity reactions and renal impairment.^[4]

Among these, the occurrences of subtrochanteric or diaphyseal fractures has been reported with long-term use of BP but is not substantiated by epidemiologic studies or prospective randomized controlled trials. Regarding the possible mechanism of subtrochanteric or diaphyseal fractures it is unclear whether it is the effect of the drug or is due to underlying osteoporosis.^[5] However, it has raised world-wide debate on two aspects, i.e., for how long the BP is to be given and potential advantages/role of BP drug holidays.

Fracture intervention trial and vertebral efficacy with risedronate therapy trials established safety and efficacy of BP for 5 years and 7 years.^[6,7] The Indian Clinical Practise guidelines also recommend the use of BP for 3-5 years.^[3]

Basis for the concept of bisphosphonates drug holidays

Bisphosphonates is analogs of pyrophosphate having a three-dimensional structure capable of chelating divalent cations such as Ca^{2+} . The BP have a strong affinity for bone, targeting especially bone surfaces undergoing remodeling and binds strongly to hydroxyapatite and remains inactive until the bone containing BP are reabsorbed half-life after incorporation into mineralized bone nearly 10 years.^[8]

Furthermore, the study of Papapoulos and Cremers, 2007^[9] showed that the skeletal binding sites for BP are unsaturable and hence that they get accumulated substantially over a period of time and continues to be released for months or years after treatment is stopped.

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Thus, it is reasonable to consider that BP accumulates in bone with some persistent protective effect after therapy is stopped.^[10] Furthermore, BP discontinuation after a long period of use has been proposed to potentially reduce the incidence of the adverse events associated with its long-term use.^[11] Thus, in view of concerns of long-term use of BP and potential advantages of its discontinuation the concept of “drug holiday” has emerged recently.

CLINICAL TRIALS SUPPORTING THE BIPHOSPHONATES DRUG HOLIDAYS

Vertebral efficacy with risedronate therapy trial depicted that incidence of new vertebral fractures in the year after discontinuation of 3 years of treatment was 46% lower in the former risedronate group in comparison to placebo.^[7]

Similarly, the results of Fracture Intervention Trial Long-term Extension (FLEX) trial suggested that for many women, discontinuation of alendronate for up to 5 years does not seem to significantly increase fracture risk.^[12]

In a meta-analysis by Brown *et al.*^[13] concluded that drug holidays should only be considered in low-risk patients and in select patients at moderate-risk of fracture after 3-5 years of therapy. Whereas, when BP are prescribed to patients at high-risk of fracture, their antifracture benefits considerably outweigh their potential for harm.

In the study of Hasegawa *et al.*^[14], authors supported the idea of a drug holiday. They reported that discontinuation of oral BP for 3 months might influence the incidence of BP related ONJ and wound healing after tooth extraction in patients receiving oral BP therapy.

Park-Wyllie *et al.*^[15] favored bisphosphonate drug holidays among older women, on treatment with a BP for more than 5 years associated with an increased risk of subtrochanteric or femoral shaft fractures.

In a study by Kostoff *et al.*^[16] more than one-third of postmenopausal women taking long-term BP therapy had low fracture risk, and over 40% of the patients were eligible for a drug holiday or discontinuation.

CLINICAL TRIALS REFUTING THE BIPHOSPHONATES DRUG HOLIDAYS

Fracture Intervention Trial Long-term Extension trial, showed that discontinuation of alendronate for up to 5 years, the anti-resorptive effect is slowly lost, mainly in the lumbar spine (about 1.5% in 5 years), as well as a slow and progressive loss of femur bone mineral density (BMD) (<3% in 5 years). Women who discontinued alendronate

after 5 years showed a moderate decline in BMD and a gradual rise in biochemical markers, but no higher fracture risk other than for clinical vertebral fractures compared with those who continued alendronate. In view of these observation, the results of study recommended women at very high-risk of clinical vertebral fractures may help by continuing beyond 5 years.^[12]

The results from the FLEX compared with women who stopped alendronate after an average of 5 years, those continuing alendronate maintained a higher BMD and greater reduction of bone turnover, showing benefit of continued alendronate treatment on BMD and bone turnover. On discontinuation of alendronate therapy, rates of change in BMD at the hip and spine resumed at the background rate.^[17]

Similarly in another recent study, patients who started a BP drug holiday developed a fracture in 5.2%. Over 4 years, there was no significant change in mean lumbar spine BMD; however, there was a significant decline in the femoral neck BMD at year 2. The study further proposed that elderly patients and those with very low BMD call for close follow-up during a drug holiday. Furthermore, the study recommended that a fracture, early significant rise in bone turnover markers, and/or a decline in BMD should call for resumption of osteoporosis therapy.^[18]

Some of the other studies also provided a similar evidence that after discontinuation of alendronate after 5 years of therapy, BMD remains stable or decreases slowly while bone turnover markers stay below baseline values for up to 5 years.^[19,20]

Among women compliant with BPs for ≥ 2 years, the risk of hip fracture was increased after discontinuation, although with higher compliance and a longer duration of preceding BP therapy, this risk was attenuated. Hip fracture incidence among women who discontinued BPs versus those who did not was 8.43 versus 4.67/1000 person years ($P = 0.016$). The adjusted hazard ratio of hip fracture/90 days following discontinuation was 1.2 (1.1-1.3). For women with higher compliance at 2 years (MPR $\geq 80\%$) or compliant for 3 years, there were no significant differences in risk associated with discontinuation thus suggesting that discontinuation is not advisable under these conditions.^[21]

RECOMMENDATIONS FOR BIPHOSPHONATES DRUG HOLIDAYS BY VARIOUS TREATMENT GUIDELINES ON OSTEOPOROSIS

Major treatment guidelines worldwide and in Indian Clinical Practice guidelines on postmenopausal osteoporosis issued

in the year 2013, no specific recommendations are made on BP drug holidays.^[3]

However, American Association of Clinical Endocrinologists guidelines suggest a drug holiday after 4-5 years of BP treatment for moderate-risk patients and 10 years for high-risk patients.^[22] Since there are minimal data on safe holiday durations thus, the follow-up BMD and bone turnover markers during a drug holiday period, and reinitiating therapy if bone density declines substantially, bone turnover markers increase, or fracture occurs is highly recommended under these guidelines.

American Society for Bone and Mineral Research recommended that the continued use or drug holidays of BPs beyond 5 years should be based on a re-evaluation carried annually, assessing factors such as BMD, particularly in the hip region and fracture history.^[23]

McClung *et al.* in their studies recommended that patients on BP who are not at high-risk for fracture are potential candidates for a drug holiday and it cannot be recommended for those with BMD in the osteoporosis range or earlier history of fragility fracture. They further proposed that because the fracture probability of therapy abates slowly after stopping the treatment, while the risk of atypical fracture appears to decrease quickly, “drug holiday” of 1-2 years should be considered after 3-5 years of BP therapy except in those patients who remain at very high fracture risk.^[24,25]

Diab and Watts proposed that the length of the drug holiday should be based on clinical judgment weighing risk benefit ration of discontinuation of BP therapy.^[10]

CONCLUSION

Although theoretically, a drug holiday may be considered as an option to decrease risks of BP while continuing the protection from fractures but the level of evidence and data supporting the concept of drug holidays is a weak. Hence, before it is recommended even in a selective group of patients who have considerably improved on therapy in terms of BMD still it require more robust research in this field.

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