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REVIEW ARTICLE

Concept of drug-holiday in bisphosphonate therapy for osteoporosis in postmenopausal women: Are we ready to recommend?

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ABSTRACT

Bisphosphonates (BP) are considered one of the important treatment options for postmenopausal osteoporosis. Subtrochanteric and diaphyseal fractures are common with the long term use of BP and this particular issue has given rise to mainly two aspects of this mode of treatment, i.e., how long one can continue with BP and potential advantages or is there any role of BP drug free days. BP accumulates in bone with some long lasting protective effects after therapy is discontinued endorses this concept of giving a drug holiday in between. Theoretically speaking, a drug free period is an option to be considered to reduce the risks of BP, continuing the protective action against osteoporosis but the level of evidence and data supporting this concept of drug holidays is weak. Hence no specific recommendations are available at present for BP drug free days in currently available treatment guidelines on postmenopausal osteoporosis. Therefore more research in this aspect in future probably would throw light in this subject.

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

These group of drugs are generally well-tolerated and safe. However, there are some adverse 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 failure [4].

Though the occurrences of subtrochanteric fractures are reported with long term use of BP, it has not been substantiated by either epidemiological studies or randomised clinical trials till date. It is still to prove whether these fractures are due to the drug or due to underlying pre-existant osteoporosis [5]. However, this type of complication has raised world -wide debate on the issue of how long BP is to be prescribed and enjoy the potential advantages / role of having a drug free period. Fracture intervention trial and vertebral efficacy with risedronate therapy trials established safety and efficacy of BP for 5 years

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and 7 years [6, 7]. The Indian Practise guidelines also recommend the use of BP for 3-5years [3].

Bisphosphonates drug free days - basis of the concept

BP is an analog of pyrophosphate having a three- dimensional structure capable of chelating divalent cat-ions such as Ca^{2+}. The BP have a strong affinity for bone, which target the bone surfaces undergoing remodelling and binds strongly to hydroxyapatite and remains inactive until the bone containing BP are reabsorbed—half-life after incorporation into mineralized bone happens to be 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 and years together after treatment is stopped. Thus, it is reasonable to assume that BP persists in bone with some continued protective effect after therapy is stopped [10]. Therefore BP discontinuation after a fairly long period of use, has been thought to be potentially reduce the incidence of its adverse effects associated with the long term use of the drug [11]. Thus in view of concerns of side effects of long term use of BP and potential advantages of its discontinuation, the concept of " drug free interval" has emerged recently.

Clinical trials that support the bisphosphonates drug free intervals

Vertebral efficacy with risedronate therapy trials depicted the 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 Longterm Extention (FLEX) trial suggested that for many women, discontinuation of alendronate for up to 5 years does not seem to significantly increase fracture risks [12].

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

Hasegawa et al [14], in their study supported the idea of drug free period. They reported that discontinuation of oral BP for 3 months might influence the BP related ONJ and wound healing after tooth extraction in patients receiving oral BP therapy.

Park-Wyllie et al [15], favoured BP 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 that refute the bisphosphonates drug free intervals

FLEX trial showed that discontinuation of alendronate for up to 5 years, the anti-resorptive effect is slowly went down, 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 5years). 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 observations, the study recommended women at very high-risk of clinical vertebral fractures may help by continuing beyond 5 years [12].

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

Chiha et al in a recent study found that patients with a BP holiday developed a fracture in 5.2%, over a period of 4 years. There was no significant change in mean lumbar spine BMD;

however there was a significant decline in the femoral neck BMD at 2 years. The study further recommended that elderly patients and those with very low BMD require a close follow-up during the drug free intervals. The study further proposed that early significant rise in bone turnover markers and/ or a decline in BMD should call for resumption of anti-osteoporosis therapy [18].

Some of the other studies also provided 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]

Recommendations for bisphosphonates drug free intervals by various treatment guidelines on osteoporosis

Majority of treatment guidelines worldwide and in Indian Clinical Practice guidelines on postmenopausal issued in the year 2013; no specific proposals are made on BP drug free intervals during therapy.

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 [21]. Since there is minimal safety data on drug free interval, the follow-up BMD and bone turnover markers should be closely monitored during the drug holiday.

American Society for Bone and Mineral Research recommended that the continued use or drug free period of BP beyond 5 years should be based on a re-evaluation done annually, assessing factors such as BMD, particularly in the hip region and fracture history [22].

Diab and Watts proposed that length of the drug free interval should be based on clinical judgement weighing risk benefit ratio of discontinuation of BP therapy [10].

Mc Clung et al, in their study recommended drug holiday of 1-2 years after 3-5years of BP therapy except in those patients who remain at very high fracture risk [23, 24].

Vishal R Tandon et al after reviewing the literature concluded that drug holidays in BP therapy needs more robust research before it can be recommended in the present scenario [25].

Conclusion

Long term BP therapy is associated with many side effects and to reduce it and at the same time getting continued benefits on bone protection, it is theoretically possible if concept of drug free interval comes into effect in clinical practice. But as of now, level of evidence and concrete data supporting it is lacking. Therefore more research needed to recommend the drug free interval, even in a selective group of patients who had considerable improvements in terms of BMD during therapy.

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