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EDITORIAL

Bisphosphonate drug holidays: we reap what we sow

S. L. Silverman[1] · J. D. Adachi[2] · E. Dennison[3] · And the International Osteoporosis Foundation Epidemiology/Quality of Life Working Group

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The concept that our patients need to interrupt or stop bisphosphonate therapy for osteoporosis after 5 years of oral bisphosphonate therapy and after 3 years of intravenous bisphosphonate therapy has gained considerable traction worldwide. It has been our observation that some physicians (and even entire health authority regions) are automatically stopping bisphosphonates in patients who are taking osteoporosis medication without consideration for the patient's risk of fracture. In addition, some physicians have mistakenly extended this concept to other antiresorptives such as raloxifene and denosumab where bone density gains are quickly lost with discontinuation.

Has this concept of a bisphosphonate holiday been useful to us as clinicians and appropriate for our patients? The concept of a drug holiday seemed logical at first, based on the pharmacokinetics of bisphosphonates and concerns about long-term adverse events. The concept became more widely discussed after long-term bisphosphonate studies such as the Fracture Intervention Trial (FIT) and Long-Term Extension (FLEX) Trial, were published [1], and the FDA published its opinion in 2011, suggesting reevaluation of the need for continued bisphosphonate therapy beyond 3–5 years in individual patients not at high risk [2]. Bisphosphonates have long-term residence in the bone [3]. This-long term residence in the bone means that after prolonged use, the bisphosphonate remains in the bone and due to reduced bone turnover is slowly excreted and recycled, resulting in a persistent but waning antiresorptive effect [4].

We have learned about the incidence of rare side effects with long-term therapy. The incidence of these side effects (osteonecrosis of the jaw [ONJ] and atypical femoral fracture [AFF]) is rare and increases with exposure with an inflection point of 4 years for ONJ [5] and 5 years for AFF. [6] The American Society for Bone and Mineral Research (ASBMR) (7) estimated ONJ incidence as between 1 in 10, 000 and less than 100,000 patient-treatment years [7]. The AAOMS [8] using data from Lo [5] estimated 210/100,000 patient years. The incidence of AFF appears related to duration of exposure. Dell [6] using radiographic review of claims data found a rate of AFF of 2/100,000 after 2 years exposure and 78/100,000 after 8 years of exposure. Schilcher (9) estimated an incidence rate of 50/100,000 person years.

Furthermore, it is not clear that BP discontinuation reduces AFF risk in the first years after discontinuation. Although one observational study estimated a 70 % reduction in risk of AFF with every year after discontinuation [9], in a subsequent more detailed report from the same group [10] it appears that this estimate, which is based on short-term drug data, is derived from a case–control analysis comparing conventional femoral shaft fractures with atypical fractures. Thus, a drug holiday could shift the balance towards typical rather than atypical

Members of the International Osteoporosis Foundation Epidemiology/Quality of Life Working Group include: B Abrahamsen, J Adachi, F Borgström, O Bruyère, P Clark, C Cooper, E Dennison, M Diaz Curiel, HP Dimai, N Harvey, M Hiligsmann, JA Kanis, E Lau, P Lips, ME Lewiecki, E Lorenc, E McCloskey, A Papaioannou, D Prieto Alhambra, S Ortolani, S Silverman, M Sosa, P Szulc, and N Yoshimura

✉ S. L. Silverman
stuarts@bhillsra.com

[1] David Geffen School of Medicine, University of California, Los Angeles; Division of Rheumatology, Cedars-Sinai Medical Center; and OMC Clinical Research Center, 8641 Wilshire Blvd, suite 301, Beverly Hills, CA 90211, USA

[2] St Joseph's Healthcare, McMaster University, Hamilton, ON, Canada

[3] MRC Life course Epidemiology Unit Southampton University and Victoria University of Wellington, Wellington, New Zealand

fractures of the femur but it does not necessarily follow from this that a drug holiday will reduce the risk of AFFs

What is the risk/benefit analysis of continuing oral bisphosphonate therapy beyond 5 years? Let us consider a thought exercise. If we look at the FLEX extension of FIT which included high risk women (defined as prior vertebral fracture or T score <−2.5), we see an approximate 5 % incidence of clinical vertebral fracture (CVF) or about 5000 CVFs over the 5 years. Continuing alendronate reduced the risk of CVF by 45 % (CI 18–64 %) thus preventing 2250 CVF. The risks of concern are ONJ and AFF. Using the Dell [6] or Schilcher [9] data, we can estimate 55 (Dell) to 126 (Schilcher)/100,000 person years of AFF at 8 years. The incidence estimates of ONJ vary from 1/10,000 or 10/100,000 (ASBMR [7]) to as high as 210/100,000 (AAOMS [10]) using data from Lo [5]). This suggests we prevent from 7 to 35 clinical vertebral fractures for every high-risk patient who has a significant adverse event of ONJ or AFF. These analyses suggest a positive risk/benefit ratio for continuing bisphosphonates in high-risk women.

We should not forget that the mortality of vertebral fractures is similar to that of hip at 3 years, and that the morbidity associated with vertebral fracture is very substantial. Thus, the benefit of bisphosphonate therapy with regard to reduced fracture incidence in moderate and high-risk women clearly outweighs the risk of rare adverse events. There are also some signals to suggest fewer deaths, although the mechanism for this needs yet to be unraveled [11, 12]. However, one must note that the data supporting these risk benefit calculations is not robust. Sample sizes are small, and there are limitations in trial design.

Randomized withdrawal studies have re-randomized patients previously enrolled in randomized controlled trials to medication or placebo after 3 years on therapy. These studies (FLEX [1], Vertebral Efficacy with Risedronate Therapy (VERT) [13] and Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON)[14] have shown BMD decreases with discontinuation but BMD remained higher than baseline and higher than former placebo patients. Of note, bone turnover markers increased [1, 13, 14]. The significance of this BMD loss is unclear.

These randomized withdrawal studies have suggested benefit of continuation of therapy in a subset of patients at higher risk. In FLEX, there were fewer clinical vertebral fractures in the long-term-treated group (55 % reduction) compared to the treated patients randomized to placebo. Patients in FLEX at high risk as defined by femoral neck T-score ≤−2.5 and no vertebral fracture had fewer subsequent non-vertebral fractures if they continued therapy. In FLEX, the number needed to treat for 5 years was 17 in women with prevalent vertebral fracture who had a femoral neck T-score <−2.0 while the number needed to treat was 24 for women without vertebral fracture and a femoral neck T-score of −2.5 or below [1]. This suggests benefit for a subset of patients through 10 years. In HORIZON, there were significantly fewer morphometric vertebral fractures in patients who continued treatment versus those randomized to placebo [14]. After 3 years of zoledronate therapy, in women who had a total hip T score above −2.5, no recent incident fracture and no more than one risk factor (almost 55 % of the population), risk for subsequent fracture (over three additional years) was low if treatment was discontinued (for morphometric vertebral fracture the average risk was 3.2 % and for non-vertebral fracture the average risk was 5.8 %). In these patients at lower risk, discontinuation for up to 3 years was considered reasonable [14]. Conversely, if a patient had a T-score less than −2.5 or had a recent vertebral fracture, then an additional 3 years of therapy was of benefit in preventing morphometric vertebral fractures although treatment beyond 6 years did not seem to offer benefit [15]. There was no benefit of long-term treatment in reducing risk of non-vertebral fractures in the treatment arms in either FLEX or HORIZON. The data on reported vertebral fracture risk reduction needs to be viewed critically with one study reporting decreased risk of clinical not morphometric vertebral fracture and one study reporting the opposite.

Can we use these long-term trials to guide our decisions about patients in our clinic? The data suggest we need to individualize the decision based on multiple risk factors: bone density, clinical risk factors, and history of incident fracture [16, 17]. There clearly are some patients at low risk who were started on bisphosphonates in the past when treatment may not have been indicated who should be discontinued. But there are many patients at moderate or high risk who may benefit from therapy continuation.

Do we have any consensus globally on the identification of patients for a bisphosphonate holiday and in the management and monitoring of the holiday? In 2014, the Epidemiology/Quality of Life Working Group of the International Osteoporosis Foundation convened a panel which voted on appropriateness of bisphosphonate holidays using the Rand UCLA appropriateness method. The panel voted appropriateness on a 1 to 9 scale. The voting revealed considerable controversy globally and a lack of consensus on identification, management, and monitoring of antiresorptive holidays. The group did agree that clinicians should not consider a holiday if a patient is at high risk as defined by lowest T-score <−3.5, on 5 mg or more glucocorticoids or a history of multiple fractures. The group could not agree on duration of the holiday or on how we could monitor our patients once on holiday. These findings reflect clinical confusion about best practice and highlight the need for further research in this area.

Do we know how to monitor a holiday once we start it? BMD changes and, therefore BMD monitoring, are not useful in predicting who will most likely benefit from continued alendronate therapy [18, 19]. The role of bone turnover markers in monitoring is unclear. We know from randomized

withdrawal studies that with continued therapy, bone turnover markers remain stable. In patients re-randomized to placebo, markers increased after discontinuation but levels remained below baseline. In FLEX in a small sample of 76 women, bone markers did not predict bone loss [18] or risk of fracture [19]. To use bone markers to monitor a holiday, we will need to know if increases in bone markers in our patients on holiday reflect bone loss.

Unfortunately, the concept of the need for an osteoporosis medication holiday reinforces a perceived danger related to osteoporosis medication. Is this perceived danger one of the factors in the continued decrease in osteoporosis medication use in the last few years [20–22]. However, we now see increasing concerns about osteoporosis therapies by our patients fed not only by concerns about rare side effects but also by their understanding that the need for holidays suggests that these drugs may be dangerous to use. Furthermore, there is now concern by our patients that all osteoporosis medications are dangerous (categorical bias).

We conclude that there are risks associated with any therapy including osteoporosis therapies. The benefits of continuing osteoporosis therapy in patients at risk of fracture exceed the risk of rare adverse events early in treatment. This benefit/risk calculation may be attenuated with time. Adherence to bisphosphonate therapy in all of the published studies has been uniformly low. Are we compounding the problem of treatment by stopping those who actually continue to adhere? Clinicians need to rethink the assumption that a patient who has taken an oral bisphosphonate for 5 years or an intravenous therapy for 3 years should automatically start a drug holiday. The clinician should individualize the decision for each patient based on their fracture risk.

Compliance with ethical standards

Conflicts of interest Dr Silverman has received grant/research support from Roche diagnostics is a consultant to Lilly, Amgen, and Pfizer and is a member of the speakers' bureau for Lilly, Pfizer, and Amgen.

Dr Dennison is a member of the Lilly speakers' bureau.

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