



Bisphosphonate holidays: using cost-effectiveness analysis for the “yes, but” questions

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Faced with advising the patient currently sitting in their exam room, clinicians reading the best available evidence are invariably left with many “yes, but” questions. When the patient is a postmenopausal woman who has just completed 3 years of zoledronic acid, the best available evidence from the HORIZON-PFT extension studies [1, 2] suggests that continuing for another 3 years, as compared to a bisphosphonate holiday, will result in a modestly higher femoral neck bone mineral density (BMD) and approximately 50% lower hazard of morphometric vertebral fracture, but no difference in clinical fractures. “Yes, but what if my patient is substantially older or younger than the median age of participants (75 years), or has already suffered a vertebral fracture? Yes, but the 95% confidence interval around the morphometric vertebral fracture risk reduction is quite wide (0.15–0.77); what if either of those extremes is the true value? Yes, but if this patient is in a Medicare Shared Risk program, what would my Health System want me to advise? What is the best strategy for society as a whole?”

A rigorous cost-effectiveness analysis is one tool that can help us answer these “yes, but” questions. Cost-effectiveness analysis is a modeling approach that incorporates best available evidence, weighs trade-offs between potential benefits and harms, and incorporates patient values by considering their reported “utilities” for various health states [3]. A range of remaining life expectancy and underlying risk can be modeled to quantify the benefits and harms in patients who differ from the average clinical trial subject. Sensitivity analyses can quantify how much the inherent uncertainty around clinical trial results impacts the attractiveness of a treatment strategy by considering the “best and worst” case 95% confidence intervals. Economic analyses also help us consider the

decision from different perspectives (patient, payer, healthcare system, society) by varying which costs and benefits are included in the model. Finally, cost-effectiveness analyses highlight areas where additional research is particularly needed.

In this issue of *Osteoporosis International*, Drs. Nayak and Greenspan offer clinicians a carefully constructed cost-benefit analysis of different lifetime strategies of zoledronic acid treatment in postmenopausal women with T-scores between -2.5 and -3.5 : recurrent periods of 3-year treatments followed by 3-year holidays (3/3 strategy), recurrent periods of 6-year treatments followed by 3-year holidays (6/3 strategy), or no treatment. They modeled women starting at ages 50, 60, 70, and 80 years and compared those with vs. without vertebral fractures at baseline and those with T-scores -2.5 vs. -3.5 at baseline. They considered the extremes of the 95% confidence intervals of the HORIZON-PFT extension study efficacy estimates. They considered scenarios in which BMD loss is more rapid during the bisphosphonate holiday. They included direct medical costs and nursing home costs. They used ranges of patient-reported utilities, reflecting how patients value living with a specific fracture type compared to full health. After running many models with millions of simulated women, the authors report that in nearly all cases, the zoledronic acid 3/3 strategy had superior cost-effectiveness and in many instances was the dominant strategy (i.e., was both least expensive and most effective). They conclude that the 3/3 strategy is likely to be more cost-effective than 6/3 and that both are more cost-effective than no treatment.

Before advising the patient waiting in our exam room, we need to identify the key model assumptions to be sure that they are supported by evidence and make sense for our context. First, the authors have taken a “payer” perspective, including direct healthcare costs, but not considering other measures of the societal burden of fractures such as informal caregiving costs and lost workforce productivity. Reporting at least 2 perspectives, including both a health sector and a societal perspective, is recommended by the Second Panel on Cost-effectiveness in Health and Medicine [4]. In this case, the 3/3 strategy was both more effective in reducing fractures

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and cheaper (dominant) in most of the authors' models such that adding societal costs would only strengthen their conclusions. However, we need to consider whether other model assumptions could impact the 3/3 models' dominance.

The authors also assumed that patients would be as adherent with annual infusions as subjects in the HORIZON-PFT and extension trials (approximately 80% and 90%, respectively) and that all survivors would re-initiate treatment cycles throughout their remaining lifetime. In real-world practice, these figures are likely to be substantially lower [5, 6]. Delays or "drop out" from restarting treatment cycles would certainly change the cost-effectiveness estimates and even potentially change the preferred treatment strategy if restart rates are low. This would be particularly true from a societal perspective and is an area for future study. The authors appropriately note that their findings should apply only to highly adherent women.

Finally, the authors have assumed that the efficacy of zoledronic acid in subsequent treatment periods is equivalent to the initial reduction observed in the HORIZON-PFT trial (i.e., 41%, 25%, and 77% reduction in hip, non-vertebral, and clinical vertebral fractures, respectively). In their models, patients in the 6/3 strategy have more morphometric vertebral fractures prevented than patients in the 3/3 strategy during years 3–6, consistent with the extension trial results. However, during years 7–9, the 3/3 group is assumed to experience the substantial reduction in multiple clinical fracture types observed in HORIZON-PFT as they restart treatment, while the 3/6 group remains on holiday. As a result of this assumption, the models yield the somewhat counter-intuitive finding that the 3/3 strategy prevents more major osteoporotic and other clinical fractures than the 6/3 strategy over sequential treatment periods. Because the costs and patient-reported utility reduction are greater for these fracture types than for the morphometric vertebral fractures prevented in the last 3 years of a 6-year treatment period, the 3/3 strategy is almost certain to dominate under this assumption. We were unable to identify published data to support or refute this important assumption; long-term clinical trials of bisphosphonates are limited to one cycle of treatment and holiday [7], cohort studies examining real-world fracture rates during drug holidays have not reported findings from subsequent treatment periods [8], and we found no reports of BMD or bone turnover marker changes during a second treatment period. The authors did perform sensitivity analysis which assumed only half the clinical fracture reduction efficacy for subsequent treatment periods, and the 3/3 strategy remained dominant. However, if clinical fracture reduction benefits are more substantially attenuated, the cost-effectiveness of both strategies would be diminished and the 6-year treatment strategy might become more cost-effective. Therefore, the assumption that efficacy is preserved in subsequent treatment periods after a holiday should be tested empirically in future randomized trials or cohort studies.

The careful analysis by Nayak and Greenspan provides valuable information for our patient's decision. We can advise her (and her insurer) with greater confidence that regardless of her age, prior vertebral fracture, or baseline BMD that taking a holiday after 3 years of zoledronic acid is likely to be the best approach *if* she is willing to engage in future treatment cycles *and* assuming that restarting zoledronic acid will result in at least half the benefit achieved in the first cycle. An important "yes, but" question remains; since we have not been able to achieve high rates of adherence to restarting bisphosphonates after a holiday in real-world practice, is a 6-year "treat them while you've got them" strategy a better general approach from a societal perspective?

Declarations

Conflicts of interest None.

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