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Continuing Bisphosphonate Treatment for Osteoporosis — For Whom and for How Long?

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In the 21st century, osteoporosis, a disease once considered an inevitable consequence of aging, is both diagnosable and treatable. Large, randomized, controlled trials have shown that bisphosphonate therapy for 3 to 4 years is effective in reducing the risk of both nonvertebral and vertebral fractures in osteoporotic women.¹ Not surprisingly, as many as one in seven postmenopausal women in the United States have been treated with a bisphosphonate at some time. However, there is considerable controversy over the ideal duration of antiresorptive therapy, particularly since reports have emerged of atypical subtrochanteric fractures as well as osteonecrosis of the jaw during prolonged bisphosphonate therapy. These concerns prompted the Food and Drug Administration (FDA) to reevaluate the efficacy of continuing bisphosphonate therapy beyond 3 to 5 years, as now described in the *Journal* article by Whitaker et al. and the agency's briefing document.¹

As Whitaker and colleagues note, there are few data available for assessing the efficacy of long-term bisphosphonate use (>5 years) in reducing the risk of fractures. Two randomized trials with a combined sample size of 2342 women provide the best evidence on which to base clinical recommendations. The bulk of the evidence regarding continuing treatment beyond 5 years derives from the Fracture Intervention Trial Long-Term Extension (FLEX), which randomly assigned 1099 postmenopausal women who had previously received an average of 5 years of daily alendronate therapy to continued alendronate treatment or placebo for an additional 5 years.² The other relevant randomized trial, the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Extension trial, used a similar design with a shorter treatment period (3 years of treatment followed by 3 years of placebo or active extension).³ The FDA reanalysis included both trials and used novel methods that differed from the original preplanned analyses of these trials.^{2,3} Both trials were conducted in post-menopausal women, and therefore results may not apply to younger women or to men.

The FDA analyses looked at a composite end point of all fractures, both vertebral and non-vertebral, and showed little benefit of continued bisphosphonate treatment beyond 5 years. The original preplanned analyses had separated vertebral and nonvertebral fractures because of their distinct pathogenesis and different responses to treatment. We have now reevaluated our analyses of these trials in order to provide clinical recommendations regarding the continuation of bisphosphonate therapy for osteoporosis. The FLEX and HORIZON extension studies used changes in bone mineral density as their primary end points and reported fractures as exploratory end points. The two studies were consistent in showing significant reductions in the risk of vertebral fracture with continuation of bisphosphonate treatment. In FLEX, the reduction was observed in clinical (symptomatic) vertebral fractures (relative risk, 0.45; 95% confidence interval [CI], 0.24 to 0.85), whereas in HORIZON, it was seen in vertebral fractures detected on paired radiographs (odds ratio, 0.51; 95% CI, 0.26 to 0.95). Neither trial showed an overall reduction in nonvertebral fractures. The confidence intervals for all fracture results were wide, reflecting the relatively small size of the trials and the small numbers of fractures. Nevertheless, taking into account the totality of evidence, we believe that the evidence regarding vertebral fractures is the most robust basis for clinical recommendations.

The table shows that in FLEX, the risk of clinical vertebral fracture among patients receiving placebo was related to bone mineral density at the femoral neck at the start of the extension trial (after 5 years of alendronate therapy), as well as to the presence of vertebral fractures at that time. The HORIZON study also confirmed that bone mineral density was predictive of vertebral fracture risk among participants who discontinued zoledronic acid treatment. Since the reduction in the risk of clinical vertebral fracture with continued alendronate therapy in FLEX was generally consistent across subgroups defined by bone mineral density at the femoral neck and the presence or absence of preexisting vertebral fracture, for the analysis presented in the table we assumed that there was no treatment interaction, although the numbers of fractures within subgroups was small and the power to detect an interaction was low.^{2,4} We used data from FLEX to estimate the number needed to treat (for 5 additional years) to prevent one clinical vertebral fracture in subgroups defined by bone mineral density at the femoral neck and by prevalent vertebral fracture status at entry in FLEX (after 5 years of initial alendronate treatment). The risk of vertebral fracture is highest and numbers needed to treat are lowest for patients with a femoral neck T score below -2.5 , which suggests that these patients may reasonably expect to benefit by continuing bisphosphonate therapy. In addition, patients with a preexisting vertebral fracture with a somewhat higher (although not higher than -2.0) T score for bone mineral density may also benefit from continuation. In the FLEX trial, 50% of patients who were receiving alendronate were assigned to continue at a dose of 5 mg per day, half the usual clinical dose of 10 mg per day; changes in bone mineral density and in markers of bone turnover and antifracture efficacy were similar in this group. Although the effect on safety of administering lower doses is unknown, these results suggest that doses lower than the usual 70 mg per week might be considered for longer-term use.

The table shows that numbers needed to treat are much higher for those with no preexisting fracture who have a femoral neck T score above -2.0 after an initial treatment period, which suggests that such women can discontinue treatment and have a relatively low risk of

subsequent vertebral fracture. This group of patients would include many of those who originally began receiving bisphosphonates when they had a bone mineral density above the osteoporotic range or for the prevention of bone loss.

For patients who have discontinued treatment after 5 years, there are currently no data to guide clinicians in determining when and whether to resume treatment. The role of repeat assessment of bone mineral density, bone turnover markers, and other clinical indicators is currently under study.

The FLEX and HORIZON trials showed that bone loss after discontinuation of therapy (the primary end point in both studies) was only modest as compared with that during continued therapy, suggesting a similarly persistent effect of alendronate (5 years) and zoledronic acid (3 years). Observational studies show that there is greater bone loss after discontinuation of risedronate therapy, and there are no data regarding effects after discontinuation of ibandronate therapy. Therefore, we believe that recommendations regarding discontinuation should be limited to alendronate and zoledronic acid.

In sum, although evidence is limited regarding the risk of fracture with the continuation of bisphosphonate therapy beyond 3 to 5 years, data from randomized, controlled trials generally suggest that the risk of vertebral fractures is reduced. On the other hand, consistent evidence of a statistically significant reduction in nonvertebral fractures with the continuation of bisphosphonates is lacking. Thus, for clinicians, we believe that the current evidence base supports the following conclusions. Patients with low bone mineral density at the femoral neck (T score below -2.5) after 3 to 5 years of treatment are at the highest risk for vertebral fractures and therefore appear to benefit most from continuation of bisphosphonates. Patients with an existing vertebral fracture who have a somewhat higher (although not higher than -2.0) T score for bone mineral density may also benefit from continued therapy. Patients with a femoral neck T score above -2.0 have a low risk of vertebral fracture and are unlikely to benefit from continued treatment. We recognize that these conclusions, which are based on reductions in vertebral fractures, might change as additional data about long-term risks of bisphosphonate therapy become available.

Not all bisphosphonates are alike, so recommendations for discontinuation of bisphosphonates need to be drug-specific. Recommendations about monitoring after discontinuation and reinitiating antifracture therapy await further studies.

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Table 1

Risk of Clinical Vertebral Fracture and Number Needed to Treat for 5 Years to Prevent One Clinical Vertebral Fracture in the Fracture Intervention Trial Long-Term Extension (FLEX) Study.*

Femoral Neck BMD T Score at Start of Extension [†]	5-Yr Risk of Clinical Vertebral Fracture		Risk Difference (95% CI)	Number Needed to Treat
	Placebo Group	Alendronate Group [‡]		
	<i>no./total no. (%)</i>			
All women in study				
All BMD T scores	23/437 (5.5)	16/662 (2.5)	2.9 (0.3–5.4)	34
Less than or equal to –2.5	11/132 (9.3)	9/190 (4.5)	4.8 (0.8–9.2)	21
Greater than –2.5 and less than or equal to –2.0	9/126 (5.8)	3/185 (2.8)	3.0 (0.3–6.7)	33
Greater than –2.0	3/179 (2.3)	4/282 (1.1)	1.2 (0.2–2.8)	81
Women with no prevalent vertebral fracture at start of FLEX study				
Less than or equal to –2.5	6/75 (8.0)	4/109 (3.8)	4.2 (0.6–9.1)	24
Greater than –2.5 and less than or equal to –2.0	3/82 (3.0)	1/121 (1.4)	1.6 (0.2–5.0)	63
Greater than –2.0	2/130 (1.8)	2/203 (0.9)	1.0 (0.1–2.6)	102
Women with prevalent vertebral fracture at start of FLEX study				
Less than or equal to –2.5	5/57 (11.1)	5/81 (5.3)	5.8 (0.8–12.1)	17
Greater than –2.5 and less than or equal to –2.0	6/44 (11.1)	2/64 (5.3)	5.8 (0.8–13.6)	17
Greater than –2.0	1/49 (3.7)	2/79 (1.7)	2.0 (0.3–5.6)	51

* The risks, risk differences, and numbers needed to treat were estimated from proportional-hazards models for the effect of treatment — first unadjusted, then adjusted for bone-mineral-density (BMD) categories, and finally adjusted for BMD categories and baseline prevalent vertebral fracture together. The 5-year risks (percentages) were derived from the proportional-hazards model and account for censoring. Confidence intervals were calculated with the use of the bootstrap method with 1000 replications. CI denotes confidence interval.

[†] The extension period began after 5 years of initial treatment.

[‡] Included are patients who received the drug at a dose of 5 mg per day and those who received the drug at a dose of 10 mg per day.