# Ten vs Five Years of Bisphosphonate Treatment for Postmenopausal Osteoporosis

## Enough of a Good Thing

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In the 10 years since the first results from the Fracture Intervention Trial (FIT) were published,[1,2] it has been relatively straightforward to know when to start bisphosphonate therapy for women with postmenopausal osteoporosis. Clear fracture reduction benefit was shown for women with prior vertebral fracture or bone mineral density (BMD) T scores of –2.5 or lower. However, the issue of when to stop bisphosphonate therapy is less clear, and clinical practice guidelines have been almost completely silent on this important decision point.[3]

Pharmacokinetic studies in both humans and animals have demonstrated that bisphosphonates bind tightly to hydroxyapatite and are retained for prolonged periods in bone, where they become locally active again when that bone packet is resorbed.[4] This property raised the possibility of both prolonged clinical effectiveness and prolonged risk of harm. Previous clinical studies showed that up to 10 years of alendronate therapy was associated with sustained increases in BMD and did not appear to be harmful,[5] somewhat diminishing the concern that long-term suppression of bone turnover could lead to an accumulation of microfractures and diminished bone strength.[6] However, these long-term data included fractures only as a safety end point. The best advice clinicians could provide to women who were tired of their complicated bisphosphonate regimen or concerned about the highly publicized risk of osteonecrosis of the jaw was that the risks of continued treatment probably were small.

The study by Black and colleagues[7] in this issue of *JAMA* provides important data that should enable clinicians to discuss the benefit side of the equation as well. This study provides the results of the Fracture Intervention Trial Long-term Extension (FLEX), in which 1099 of the original FIT participants who had received alendronate for approximately 5 years were randomized a second time to receive an additional 5 years of alendronate or placebo. Women who participated in FIT were excluded from continuing into FLEX if they had extremely low T scores (<–3.5) or BMD lower than their FIT baseline values. The investigators showed that women who switched to placebo after 5 years of alendronate lost a statistically significant but clinically small amount of bone density, with losses of approximately 2% to 3% more than those who continued taking alendronate for a full 10 years. In both groups, BMD remained well above FIT baseline values at the femoral neck, trochanter, and lumbar spine. Similar to previous long-term bisphosphonate trials, there was no excess of adverse events in the 10-year treatment group, and no cases of osteonecrosis of the jaw were reported. A small number of histomorphometry specimens (n=18) showed dual labeling in both groups, providing some reassurance that oversuppression of bone turnover was not seen during prolonged therapy with bisphosphonates.

More clinically interesting were the "exploratory" fracture end points. Despite the small difference in BMD between the groups, there was no excess in all clinical fractures or morphometrically detected vertebral fractures among women who stopped alendronate therapy after 5 years. There was a significant 2.9% absolute risk increase in clinically detected vertebral fractures in the placebo group, indicating that 34 women would need to be treated for an additional 5 years to prevent 1 clinically apparent vertebral fracture. The trial was powered to detect bone density changes rather than fractures. A post hoc power calculation based on a 20% incidence of fracture in the placebo group indicated that the trial had 80% power to detect a relative risk reduction of 13.5% to 33%. Thus, a 6% absolute risk increase in all clinical fractures could have occurred without detection. However, the consistency of the relative hazard ratios around 1.0 for all types of nonvertebral fractures is reassuring that no "trend" toward decreased nonvertebral fracture in the 10-year treatment group exists. It appears that for some women, 5 years of bisphosphonate therapy may be enough to realize fracture reduction benefits.

But which women are they? Because the BMD threshold that defines osteoporosis was changed during the FIT trial, 3 important subgroups of women were enrolled: those with a baseline vertebral fracture, those with baseline osteoporosis (femoral neck T score ≤–2.5) but without a vertebral fracture, and those without osteoporosis. FIT showed clear fracture reduction benefits for the first 2 groups but not the latter group.[1,2,8] The FLEX study found no significant group × treatment interaction for any of

**See also p 2927.**

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these subgroups, although the weakness of this statistical test limits the confidence that no important subgroup effects exist. When the risks of fracture in the various subgroups are examined, the greatest absolute reductions in clinical vertebral fractures (3.6%-4%) occurred in women with T scores of –2.5 or lower at the beginning of FLEX (relative risk, 0.57; 95% confidence interval, 0.23-1.40) and those with baseline vertebral fracture (relative risk, 0.47; 95% confidence interval, 0.19-1.10).

The authors reasonably conclude that women who are at high risk of vertebral fracture because of previous vertebral fractures might be considered for continued therapy. Previous nonvertebral fracture, another major risk factor for additional clinical fractures, was a stratification variable in FLEX, but the fracture results are not reported for this important population. Although a long-term study powered on fractures rather than BMD would ideally provide the best information to guide treatment decisions among these subgroups, such a study would be extraordinarily expensive. The FLEX trial therefore provides the best data likely to be available on this question.

The FLEX trial has several important clinical implications. First, women who have a good response to 5 years of bisphosphonate therapy (3%-5% increase in hip BMD, 8%-10% increase in spine BMD, and T score >–3.5) and are not otherwise at increased risk of vertebral fracture can consider a "holiday" period of up to 5 years without therapy. This strategy would clearly improve the reported cost-effectiveness of bisphosphonates.[9,10] However, the importance of careful BMD monitoring is increased in such women; those rapidly losing BMD (in FLEX, the thresholds were >8% in 1 year, >10% in 2 years, or >5% from baseline) will likely require resumption of bisphosphonate therapy or a switch to an alternative agent.

Clinicians must bear in mind that substantial differences in absolute BMD and T scores may result when different brands of dual-energy x-ray absorptiometry machines are used for serial testing in the same patient, and that measurement error can be a significant problem in some test centers.[11] Thus, it is important to use a reliable center and the same machine whenever possible. An alternative to frequent BMD measurement might be to observe serum markers of bone turnover. In the FLEX trial, increases in these markers in the treatment and control groups mirrored changes in BMD, and higher bone turnover marker levels have previously been associated with a greater antifracture effect of bisphosphonates.[12] This strategy would, however, require validation and establishment of decision cut points before it could be clinically useful. It is unclear at this time whether resuming bisphosphonate therapy in women at the end of their "holiday," or when their BMD has declined below a given threshold, would result in additional fracture reduction benefit. Decisions about additional treatment should consider the individual fall risk, individual fracture risk, response to previous therapies, and remaining life expectancy.

Findings from FIT and similar trials established that starting bisphosphonate therapy in postmenopausal women with osteoporosis or a low-trauma fracture substantially reduces their risk of vertebral and nonvertebral fractures, pain, and disability.[13] Now, armed with FLEX data, physicians may be able to begin telling women when they have had enough of a good thing.

**Financial Disclosures:** Dr Colón-Emeric reports that she has received research funding and consultancy funding from Novartis Pharmaceuticals.

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