

## COMMENTARIES

### Bisphosphonate Therapy: To Stop or Not to Stop?

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**Commentary on:** Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, Satterfield S, Wallace RB, Bauer DC, Palermo L, Wehren LE, Lombardi A, Santora AC, Cummings SR; FLEX Research Group. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA*. 2006 Dec 27;296(24):2927-38.

Bisphosphonate therapy is now the mainstay of treatment for patients with primary and secondary forms of osteoporosis. This class of drugs has earned this role because of multiple studies documenting the reduction in the incidence of vertebral and other fragility fractures in older women with osteoporosis at moderate to high fracture risk and the prevention of bone loss in many other medical conditions with bisphosphonate therapy (1). After beginning therapy, clinicians then confront the question of how long therapy should be continued. Unless there are obvious safety issues, long-term therapy is generally planned for chronic degenerative disorders such as osteoporosis. Such therapy with bisphosphonates poses unique challenges. The drugs accumulate in the skeleton, theoretical concerns about the safety of long-term treatment with potent inhibitors of bone remodeling exist, and there are suggestions that significant clinical benefit persists well beyond the treatment interval (2-4). Needed is a study in which important clinical outcomes are assessed in patients who have been on bisphosphonate therapy for several years and who then either continue or discontinue treatment. The recent FLEX study by Black and colleagues provides much of that information and is the most comprehensive set of data we have to determine whether there is value or harm in continuing alendronate therapy beyond 3-6 years (5). Even with these

**results, there will be debate about the need for and safety of long-term bisphosphonate treatment.**

There are several components to the question of whether therapy should be continued or stopped after a finite interval:

*1. Do the effects of treatment persist with continued use or do patients ultimately escape the effects of treatment?*

There is strong and consistent evidence that the anti-remodeling effects of bisphosphonate therapy, assessed by biochemical indices of bone turnover or by histomorphometry, persist for at least seven years with risedronate and ten years with alendronate, and no evidence suggests that patients become refractory to treatment (4;6). However, the objective of osteoporosis treatment is to protect patients from the occurrence of fragility fractures. Direct evidence for the reduction in fracture risk has been demonstrated for only 3 years with ibandronate, 4 years with alendronate and 5 years with risedronate, while less direct evidence suggests that the effectiveness of risedronate persists for up to 7 years (6-8).

*2. Are there safety concerns with long-term use?*

In clinical trials, the bisphosphonates are consistently well tolerated, and no non-skeletal adverse events have been reported in long-term studies that were not recognized in the early short-term trials. Theoretical concern about possible over-

suppression of bone turnover with potent anti-remodeling drugs has existed since the early studies with alendronate (9). Bone remodeling declines but then reaches a nadir within a few months of beginning bisphosphonate therapy, and no study has demonstrated progressive inhibition of bone remodeling with prolonged treatment (4;6;7). The average rate of bone remodeling observed on bisphosphonate therapy is similar to that observed with estrogen therapy, and no issues about bone safety have been noted with long-term estrogen treatment (10;11). Clinical states of low bone remodeling such as hypoparathyroidism have not been associated with untoward skeletal effects (12). Furthermore, bone remodeling is not maximally suppressed with the clinical doses of alendronate. Additional suppression of bone resorption is observed when estrogen therapy is combined with alendronate (10;11).

Unusual and poorly healing fractures and histomorphometric evidence of very low bone formation (but not bone resorption) have been reported in patients receiving alendronate (3). Non-healing lesions of the jaw have been described in patients receiving oral bisphosphonate therapy for osteoporosis in addition to patients receiving intravenous bisphosphonate therapy for cancer-related bone disease (13). These reports stoke the concern about long-term bisphosphonate safety.

### *3. What happens when treatment is discontinued?*

Do patients revert to their pretreatment state, or are there benefits of treatment that continue after treatment is stopped? The answer to this question with drugs like beta blockers, insulin, and thyroxine are quite obvious. The effects of treatment quickly dissipate, the clinical features that have been controlled re-emerge, and no lasting benefit is noted. The issues are much more complex with bisphosphonates. The drugs accumulate in the skeleton and reside there for many years (2). The stored drug is not on the bone surface and is not available to inhibit osteoclast activity. However, release of the drugs by continued remodeling would

allow "recycling" of the drug and persistent metabolic effects (14). Additionally, bisphosphonates affect osteocyte function and apoptosis, and these effects could possibly be responsive to the drug stored in the bone (15). These considerations pose the possibility that the effects of bisphosphonate therapy could be long-lasting after discontinuation, a phenomenon that could be either beneficial or harmful. Clinical experience suggests that persistent inhibition of bone resorption occurs for perhaps a few years when alendronate at doses of 10 mg daily or higher is discontinued (10;11;16;17). The response of bone turnover after stopping 5 mg daily is less clear. Turnover markers either remain slightly lower than or return to the values in untreated patients within a year of stopping treatment (17;18). The latter data are reminiscent of the effects observed when therapy with risedronate 5 mg daily is discontinued in young postmenopausal women (19). The responses to discontinuing treatment with alendronate are clearly distinct from the rapid increase in bone resorption when estrogen therapy is stopped (10;18).

None of these previous studies have been large enough to evaluate the effects of stopping therapy on fracture risk. To address this question, we need to know whether there are differences in fracture rates between patients exposed to continuous treatment and those in whom therapy is stopped after a defined interval of treatment. The FLEX study comes close to fulfilling this need (5). One thousand ninety-nine postmenopausal women with low bone mass or osteoporosis who had received alendronate for 3-6 years (mean of about 5) were randomly assigned to continue either 5 or 10 mg alendronate daily for an additional 5 years or to discontinue treatment. Those who stopped therapy experienced modest decreases in BMD at the lumbar spine and proximal femur and modest increases in biochemical indices of bone resorption and formation. Neither BMD nor biochemical markers returned to baseline levels. These data confirm that patients do not become resistant to the anti-remodeling effects of bisphosphonates over 10 years.

The important comparison of the fracture incidence in patients withdrawn from therapy with that in women who continued to receive either dose of alendronate was an exploratory post-hoc analysis. Three sets of fracture data are provided: clinical and morphometric vertebral fracture and nonvertebral fracture. As often occurs when more than one outcome is evaluated, the results of the three sets of data are not clearly consistent. The incidence of clinical vertebral fractures was higher in those who stopped therapy, arguing strongly that continuing treatment is better than stopping. However, the nonvertebral fracture rate was identical in the two groups, suggesting just as strongly that there was no benefit in continuing treatment compared to stopping.

Which of these results is more convincing? With the exception of vertebral fracture, non-skeletal risk factors such as falls and frailty are important determinants of fracture risk. If the non-skeletal risk factors are not affected by antiresorptive therapy, the ability to detect an effect of bone-strengthening treatment in fracture risk is blunted. Protection from nonvertebral or hip fracture has been documented with bisphosphonate therapy only in postmenopausal women with clear evidence of osteoporosis, diagnosed either by pre-existing vertebral fracture or BMD values that meet the criteria for diagnosis (8;20;21). Many women in FLEX did not have osteoporosis by those criteria, perhaps limiting the ability to evaluate the effectiveness of treatment on nonvertebral fracture risk.

The clinical vertebral fracture outcome may be the least robust of the three fracture endpoints. The ascertainment of clinical vertebral fracture involves significant variables and uncertainties, especially when this outcome is not a predefined endpoint with a clear and consistent definition. Whether a patient experienced a "clinical" vertebral fracture depends upon the sensitivity of the patient to her symptoms and of the clinical investigator to the patient's complaints.

Morphometric vertebral fractures are the most appealing outcome and could serve as

the "tie-breaker" set of data. This has been the primary endpoint in almost all of the major fracture prevention studies. Vertebral fracture is the quintessential fragility fracture and is less influenced by frailty and trauma than are hip and wrist fractures. All patients had similar predefined evaluations with paired spinal X-rays at the beginning and end of the FLEX study. Unfortunately, these results are indeterminate. A modest but statistically insignificant reduction in risk was observed in those who remained on therapy. It is unlikely that the results would have been clearer had all patients received 10 mg daily, for no difference in morphometric vertebral fracture incidence was observed in women receiving either 5 mg or 10 mg daily for 3 years (22).

The FLEX results leave us with substantial uncertainties regarding our clinical question. We can conclude that stopping alendronate therapy after 3-6 years is justified in patients at low or moderate risk of fracture. We can also conclude, with equal conviction, that patients at high risk are better served by remaining on therapy. The most important conclusion from FLEX is that there was no suggestion of skeletal harm with continued treatment. No signal of increased fracture rates with continued therapy was observed, and no new safety concerns with long-term treatment were noted, consistent with data from other long-term treatment studies.

Even these limited results cannot be extrapolated to other bisphosphonates, alternate dosing regimens including intravenous dosing, or other clinical conditions such as osteoporosis associated with glucocorticoid therapy. Despite these limitations, the FLEX study is the best prospective data we will have regarding the long-term safety of oral bisphosphonates.

As much as we wish for firm evidence upon which to base our clinical decisions, we are left with the need to make many decisions with clinical judgment. We must tailor therapy to the needs of our individual patients, being both thoughtful and flexible in our approaches to patient care.

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