PERSPECTIVES

Long-Term Use of Alendronate

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The bisphosphonate alendronate has been in clinical use for almost a decade. Its beneficial effects on bone density and turnover are now everyday clinical observations, and its antifracture efficacy has been demonstrated in a number of clinical trials. The first of these was extended from its original endpoint of three years (in stages) to 10 years (1). The data demonstrate progressive increases in bone density over this period of time, with sustained (but nonprogressive) suppression of bone turnover. Fracture data from the extension trial are scanty, but certainly do not show any acceleration of fracture rate with long-term therapy and are suggestive of sustained benefit.

The Fracture Intervention Trial (FIT), a second major alendronate study, was also extended. In the extension trial, called FLEX,1099 women (age range, 60-86 years), who were assigned to alendronate in FIT and had an average duration of use of five years, were rerandomized as follows: 30% received alendronate (10 mg/day), 30% received alendronate (5 mg/day), and 40% received placebo for an additional five years. All participants were encouraged to take calcium and vitamin D.

BMD and turnover data for the first three years of the FLEX extension trial have been published (2) and show that total hip BMD decreased by 2.4% in the placebo group (reaching a level that was still more than 1% above the FIT baseline), compared with 0.4% in the combined alendronate groups. In the extension trial, BMD increased in the spine by 1.0% in the placebo group, but by 3.5% in the group that continued active therapy. Bone density changes were 0.5% to 1.0% more positive in subjects on alendronate 10 mg/day than in those on alendronate 5 mg/day. Bone alkaline phosphatase level increased about 15%, urinary N-telopeptide excretion, about 20%, in those rerandomized to placebo during the extension trial ($p < 0.001$ for both); however, N-telopeptide excretion remained 60% lower than the level seen at the beginning of the FIT study.

Data have now been presented for the five-year endpoint of the FLEX extension trial (3). BMD changes at this endpoint were similar to those at three years (hip BMD: placebo –3.4%, alendronate –1.0%; spine BMD: placebo 1.5%, alendronate 5.3%). Most importantly, available fracture data also showed a relative risk of 0.45 for clinical spine fracture, but 1.0 for nonspine fracture, if subjects continuing on either dose of alendronate were compared with those receiving placebo. This finding indicates that continuation of alendronate for 10 years produces a more beneficial fracture outcome than does its discontinuation after only five years - a major reassurance to the many osteoporotic patients around the world who are taking this drug and to the physicians who are prescribing it.

The authors suggest that continuous use of alendronate for up to 10 years is both safe and effective. However, the data do raise important questions regarding the long-term management of osteoporosis with alendronate and other bisphosphonates. The continuing increase in spine bone density with long-term use implies that alendronate has progressive effects on bone, and it seems that there is a progressive accumulation of bisphosphonates in bone mineral. Therefore, it is possible that at some point,

its effect will become deleterious. On the other hand, the offset data discussed above, together with similar data from other alendronate trials (4;5), suggest that even after alendronate is discontinued, bone turnover remains partially suppressed for several years. One would expect such suppression to be associated with a sustained reduction of fracture risk, but this has not been proven.

On the basis of these findings, several courses are open. One course is to conclude that treatment for up to 10 years is safe and effective, and thus, to continue most patients on treatment for this period of time; this course is supported by both of the studies discussed above. A second course is to reduce the alendronate dose from 10 mg/day to 5 mg/day (or its equivalent) in patients who have been taking alendronate for more than five years. This course is consistent with the FIT extension trial, which does not seem to show a fracture advantage with alendronate 10 mg/day over 5 mg/day during the second quinquennium of treatment; however, a detailed breakdown of the data by dose is not yet available. A third course is suggested by the recent analysis of the relationship between fracture incidence and bone resorption in risedronate studies (6). Pooling placebo and risedronate groups, there was an almost linear relationship between fracture incidence and bone resorption markers, down to marker values that were 1.5 SD below the premenopausal mean. At that point, fracture incidence seemed to plateau, suggesting that the intermittent use of bisphosphonates to maintain turnover at such a level might produce maintenance of fracture prevention; however, there is no data to address this in the context of use for five to10 years or in direct comparison with other treatment strategies.

In recent years, the general consensus has been that the surrogate endpoints of bone density and bone turnover do not guarantee antifracture efficacy. Therefore, it is not possible to determine which of the above courses is optimal in terms of fracture, the one endpoint that really does matter. The least speculative course would seem to be to continue alendronate until year 10 and then consider dose reduction, along with monitoring of bone density and turnover. Unfortunately, there is no prospect of authoritative data beyond 10 years becoming available in the foreseeable future.

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