Zoledronic Acid – Does It Have Anabolic as Well as Anti-Resorptive Effects?

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Zoledronic acid is the most recent bisphosphonate to be approved for treatment of osteoporosis in postmenopausal women. It is a third generation aminobisphosphonate with higher binding affinity to bone mineral and greater inhibition of farnesyl diphosphate synthase than any other bisphosphonate in clinical use. In clinical trials, once yearly intravenous infusion of 5 mg for three years resulted in 70%, 25% and 41% reductions in morphometric vertebral, non-vertebral and hip fractures, respectively, in postmenopausal women with osteoporosis (1). In addition, once yearly zoledronic acid was shown to reduce clinical fractures by 35% in men and women who had recently sustained a hip fracture, a benefit that was associated with a significant reduction in mortality (2).

Using conventional bone histomorphometry and microCT, Recker et al. have investigated indices of bone remodeling and structure in biopsies obtained from 152 women after three years of zoledronic acid or placebo (3). This was an unpaired biopsy design, and thus differences between the treatment and placebo group have to be interpreted in the light of whether or not age-related changes would be expected to occur in placebo-treated women. As expected, indices of bone turnover were much lower in zoledronic acid-treated women than in the placebo group, with a longer total remodeling period and resorption period. Measurement of bone volume and structural indices indicated preservation of cancellous bone mass and microarchitecture. From a bone safety viewpoint, there was no evidence of defective mineralization, marrow fibrosis, woven bone or cellular toxicity in biopsies from women treated with zoledronic acid.

An unexpected finding in the study of Recker et al. (3) was that the mineral apposition rate (MAR) was significantly higher in women treated with zoledronic acid than in those treated with placebo, regardless of whether concomitant osteoporosis medication had been used during the trial. MAR is generally regarded as an index of the activity of individual osteoblasts, although it may also be affected by the number of osteoblasts present within the BMU, and does not show significant age-related changes (4). In humans, effects of other bisphosphonates on MAR have not been consistently demonstrated whereas in animals, some studies have shown reductions in MAR (5;6). Does this mean that zoledronic acid differs from other bisphosphonates in its effects on osteoblast activity, or are there other explanations for the apparent zoledronate-induced increase in MAR?

Measurement of MAR requires identification of double tetracycline labels and is calculated as the mean distance between the labels divided by the number of days between the administration of the two labels prior to biopsy (typically 10-12 days) (7). If only single labels are present, MAR cannot be measured and it has been suggested that in such cases a low value of 0.3 µm/d should be adopted (8). This is based on the...
assumption that even in biopsies in which only single label is present, apposition is likely to be occurring but may not be detected in a relatively small number of biopsy sections for several reasons, including sampling variance, intermittent pauses in remodeling (the “on-off phenomenon”) and label escape, when mineralization starts before the first label is given or finishes between administration of the two labels. This assumption is reasonable in normal bone but may be less robust if remodeling is greatly suppressed. In the analysis of zoledronic acid-induced effects, biopsies with only single label in cancellous bone (21/59 in the zoledronic acid group and 4/52 in the placebo group) were omitted for calculation of MAR and thus the mean value, obtained from the remaining biopsies, is likely to have been overestimated, particularly in the treatment group. The increase in wall width and trabecular width that might have been expected as a result of increased MAR was not seen; however, the length of the remodeling cycle and its prolongation with bisphosphonate therapy would reduce the likelihood of demonstrating these differences after only three years of treatment.

Notwithstanding the possible effect of exclusion of biopsies with single label only on MAR in the study of Recker et al., data from some studies with other bisphosphonates indicate that the observed effect on MAR may be real. In a cross-sectional study of the effects of alendronate on bone remodeling in which double tetracycline labelling was present in all but two biopsies (one in the treatment group and one in the placebo group), in women treated with 20 mg of alendronate for 2 years and 5 mg/day for one year, the group with the highest cumulative dose, MAR was significantly higher than in the placebo group (9). In a paired biopsy study in postmenopausal women treated with risedronate for 36 months, no significant changes were seen in MAR in either the placebo or treatment group, double label being detectable in all biopsies in this study (10). Finally, the effects of daily and intermittent oral ibandronate were examined in biopsies obtained after 22 or 34 months of treatment (11). Double tetracycline labels were identified in all cases; after 22 months of treatment, ibandronate 2.5 mg daily (but not 20 mg intermittently) was associated with a significantly higher MAR than in the placebo group. After 34 months of treatment, MAR was numerically higher in both treatment groups when compared to placebo and this difference was statistically significant in the 20 mg intermittent group. Collectively, these results suggest that the more potent bisphosphonate regimens (which might be a function of the individual bisphosphonate and/or the dose used) are associated with increased osteoblast activity. Similar findings have been reported with estrogen therapy in postmenopausal women. Conventional HRT regimens are not associated with increased MAR, but high doses of estradiol given long-term result in an increase in MAR, wall width and trabecular width (12). In both cases, anti-apoptotic effects on osteoblasts provide a potential explanation. A wide range of bisphosphonates has been reported to reduce apoptosis of both osteoblasts and osteocytes (13), and this may be one mechanism by which these drugs exert beneficial effects in glucocorticoid-induced osteoporosis (14). Stimulatory effects of bisphosphonates on osteoblast cell function have also been reported in vitro in cell culture systems (15;16).

Another unexpected finding in the study of Recker et al. was the absence of any difference in the mean degree of matrix mineralization between biopsies in zoledronic acid- and placebo-treated women after 3 years. Studies with other anti-resorptive agents have generally demonstrated a higher matrix mineralization than in untreated biopsies, as would be expected since the reduction in remodeling rate increases the time available for secondary mineralization (17-20). As Recker et al. suggest, the most likely explanation for the different finding in their study is methodological; they used a microCT-based method whereas others have used quantitative backscattered electron imaging, quantitative microradiography or microCT with synchrotron radiation.

The degree of suppression of bone turnover induced by anti-resorptive agents differs
considerably and may have implications both for efficacy and long-term safety. Judged on the mean values for activation frequency, the suppression of bone turnover induced by zoledronic acid was similar to and no greater than that reported for ibandronate and alendronate. However, since the 21 biopsies with no double labelling in cancellous bone were not included in the calculation of mean activation frequency, this value would again be likely to be an overestimate. The absence of double label in cancellous bone in over one-third of biopsies from women treated with zoledronic acid contrasts with its presence in all but one of the biopsies obtained from alendronate-treated women after 2 or 3 years (9); comparison with studies in risedronate- and ibandronate-treated women is not possible since double labelling in cortical and cancellous bone was not reported separately (10;11). There are therefore some indications that zoledronic acid may induce greater suppression of the remodeling rate than other bisphosphonates at the doses used for treatment of osteoporosis.

What conclusions can be drawn from this study? First, the results confirm the potent anti-resorptive effect of zoledronic acid, and it is tempting to speculate that the impressive anti-fracture efficacy demonstrated in the HORIZON study might be related to the powerful suppression of bone turnover induced by the drug. Second, there may be moderate stimulatory effects on osteoblast activity. However, while this is of considerable interest from a mechanistic point of view, a positive remodeling balance will have little impact on bone volume if the remodeling rate is low. Third, over the three-year period of the study, no adverse effects on bone safety were observed. Finally, the data obtained emphasize the unique value of bone histomorphometry as a tool for understanding the mechanisms by which drugs affect bone remodeling and structure.

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References


histomorphometric indices of turnover. 