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COMMENTARIES

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

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Commentary on: Recker RR, Delmas PD, Halse J, Reid IR, Boonen S, García-Hernandez PA, Supronik J, Lewiecki EM, Ochoa L, Miller P, Hu H, Mesenbrink P, Hartl F, Gasser J, Eriksen EF. Effects of intravenous zoledronic acid once yearly on bone remodeling and structure. *J Bone Miner Res*. 2008 Jan;23(1):6-16.

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

1. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Caminis J, Tong K, Rosario-Jansen T, Krasnow J, Hue TF, Sellmeyer D, Eriksen EF, Cummings SR; HORIZON Pivotal Fracture Trial. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Eng J Med*. 2007 May 3;356(18):1809-22.

2. Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, Hyldstrup L, Recknor C, Nordsletten L, Moore KA, Lavecchia C, Zhang J, Mesenbrink P, Hodgson PK, Abrams K, Orloff JJ, Horowitz Z, Eriksen EF, Boonen S; HORIZON Recurrent Fracture Trial. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Eng J Med*. 2007 Nov 1;357(18):1799-809.

3. Recker RR, Delmas PD, Halse J, Reid IR, Boonen S, García-Hernandez PA, Supronik J, Lewiecki EM, Ochoa L, Miller P, Hu H, Mesenbrink P, Hartl F, Gasser J, Eriksen EF. Effects of intravenous zoledronic acid once yearly on bone remodeling and structure. *J Bone Miner Res*. 2008 Jan;23(1):6-16.

4. Parfitt AM, Villanueva AR, Foldes J, Rao DS. Relations between histologic indices of bone formation: implications for the pathogenesis of spinal osteoporosis. *J Bone Miner Res*. 1995 Mar;10(3):446-73.

5. Iwata K, Li J, Follet H, Phipps RJ, Burr DB. Bisphosphonates suppress periosteal osteoblast activity independently of resorption in rat femur and tibia. *Bone*. 2006 Nov;39(5):1053-8.

6. Lafage MH, Balena R, Battle MA, Shea M, Seedor JG, Klein H, Hayes WC, Rodan GA. Comparison of alendronate and sodium fluoride effects on cancellous and cortical bone in minipigs. A one-year study. *J Clin Invest*. 1995 May;95(5):2127-33.

7. Parfitt AM, Drezner MK, Glorieux FH, Kanis JA, Malluche H, Meunier PJ, Ott SM, Recker RR. Bone histomorphometry: standardization of nomenclature, symbols and units. Report of the ASBMR Histomorphometry Nomenclature Committee. *J Bone Miner Res*. 1987 Dec;2(6):595-610.

8. Foldes J, Shih MS, Parfitt AM. Frequency distributions of tetracycline-based measurements: implications for the interpretation of bone formation indices in the absence of double-labeled surfaces. *J Bone Miner Res*. 1990 Oct;5(10):1063-7.

9. Chavassieux PM, Arlot ME, Reda C, Wei L, Yates AJ, Meunier PJ. Histomorphometric assessment of the long-term effects of alendronate on bone quality and remodeling in patients with osteoporosis. *J Clin Invest*. 1997 Sep 15;100(6):1475-80.

10. Eriksen EF, Melsen F, Sod E, Barton I, Chines A. Effects of long-term risedronate on bone quality and bone turnover in women with postmenopausal osteoporosis. *Bone*. 2002 Nov;31(5):620-5.

11. Recker RR, Weinstein RS, Chesnut CH 3rd, Schimmer RC, Mahoney P, Hughes C, Bonvoisin B, Meunier PJ. Histomorphometric evaluation of daily and intermittent oral ibandronate in women with postmenopausal osteoporosis: results from the BONE study. *Osteoporos Int*. 2004 Mar;15(3):231-7.

12. Vedi S, Purdie DW, Ballard P, Bord S, Cooper AC, Compston JE. Bone remodeling and structure in postmenopausal women treated with long-term, high-dose estrogen therapy. *Osteoporos Int*. 1999;10(1):52-8.

13. Plotkin LI, Weinstein RS, Parfitt AM, Roberson PK, Manolagas SC, Bellido T. Prevention of osteocyte and osteoblast apoptosis by bisphosphonates and calcitonin. *J Clin Invest*. 1999 Nov;104(10):1363-74.

14. Canalis E, Bilezikian JP, Angeli A, Giustina A. Perspectives on glucocorticoid-induced osteoporosis. *Bone*. 2004 Apr;34(4):593-8.

15. von Knoch F, Jaquiery C, Kowalsky M, Schaeren S, Alabre C, Martin I, Rubash HE, Shanbhag AS. Effects of bisphosphonates on proliferation and osteoblast differentiation of human bone marrow stromal cells. *Biomaterials*. 2005 Dec;26(34):6941-9.

16. Pan B, To LB, Farrugia AN, Findlay DM, Green J, Gronthos S, Evdokiou A, Lynch K, Atkins GJ, Zannettino AC. The nitrogen-containing bisphosphonate, zoledronic acid, increases mineralisation of human bone-derived cells in vitro. *Bone*. 2004 Jan;34(1):112-23.

17. Boivin GY, Chavassieux PM, Santora AC, Yates J, Meunier PJ. Alendronate increases bone strength by increasing the mean degree of mineralization of bone tissue in osteoporotic women. *Bone*. 2000 Nov;27(5):687-94.

18. Boivin G, Vedi S, Purdie DW, Compston JE, Meunier PJ. Influence of estrogen therapy at conventional and high doses on the degree of mineralization of iliac bone tissue: a quantitative microradiographic analysis in postmenopausal women. *Bone*. 2005 Mar;36(3):562-7.

19. Roschger P, Rinnerthaler S, Yates J, Rodan GA, Fratzl P, Klaushofer K. Alendronate increases degree and uniformity of mineralization in cancellous bone and decreases the porosity in cortical bone of osteoporotic women. *Bone*. 2001 Aug;29(2):185-91.

20. Borah B, Ritman EL, Dufresne TE, Jorgensen SM, Liu S, Sacha J, Phipps RJ, Turner RT. The effect of risedronate on bone mineralization as measured by micro-computed tomography with synchrotron radiation: correlation to

histomorphometric indices of turnover. *Bone*. 2005 Jul;37(1):1-9.