

## COMMENTARIES

### Antiresorptive Agents Differ in Their Mode of Action and Morphological Effects

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#### Commentary on:

- Fuchs RK, Faillace ME, Allen MR, Phipps RJ, Miller LM, Burr DB. Bisphosphonates do not alter the rate of secondary mineralization. *Bone*. 2011 Oct;49(4):701-5.
- Allen MR, Turek JJ, Phipps RJ, Burr DB. Greater magnitude of turnover suppression occurs earlier after treatment initiation with risedronate than alendronate. *Bone*. 2011 Jul;49(1):128-32.
- Eastell R, Nagase S, Ohyama M, Small M, Sawyer J, Boonen S, Spector T, Kuwayama T, Deacon S. Safety and efficacy of the cathepsin K inhibitor ONO-5334 in postmenopausal osteoporosis: the OCEAN study. *J Bone Miner Res*. 2011 Jun;26(6):1303-12.
- Fitzpatrick LA, Dabrowski CE, Cicconetti G, Gordon DN, Papapoulos S, Bone HG 3rd, Bilezikian JP. The effects of ronacaleret, a calcium-sensing receptor antagonist, on bone mineral density and biochemical markers of bone turnover in postmenopausal women with low bone mineral density. *J Clin Endocrin Metab*. 2011 Aug;96(8):2441-9.

There are interesting principles of remodeling arising, but not necessarily directly addressed, in four papers published recently (1-4). Bone formation by the osteoblasts of the bone multicellular unit (BMU) does not instantaneously refill the resorption cavity excavated by the osteoclasts of that BMU. The delay between the completion of bone resorption and completion of bone formation is the result of the reversal phase, osteoid deposition, primary and then secondary mineralization, all of which occur more slowly than the resorptive phase (5). This normal delay produces a transient (reversible) remodeling deficit in bone matrix volume and its mineral content (6).

In morphological terms, this remodeling transient consists of the excavated volume, osteoid prior to primary mineralization and osteoid that has undergone primary mineralization but incomplete secondary

mineralization. Secondary mineralization, the enlargement of hydroxyapatite crystals within the collagen fibrils by displacement of water without change in fibril volume, may take over 12 months to reach completion and is part of the remodeling transient.

At any time during steady state remodeling, there exists this reversible remodeling deficit comprising the above morphological features. The higher the steady state remodeling, the larger the transient remodeling space deficit. Indeed, when remodeling intensity is high, osteons may never achieve full secondary mineralization because the intense remodeling removes and replaces these osteons with newly formed osteons in earlier stages of secondary mineralization. The size of this deficit has important implications in understanding the effects of drug therapy on bone morphology.

Bisphosphonates reduce the intensity of remodeling, allowing secondary mineralization of osteons (formed weeks to months earlier) to go to completion rather than being removed (7). Fuchs *et al.* report that the tempo of this mineralization is not more rapid during bisphosphonate treatment (1). The rate of mineralization did not differ between alendronate or risedronate, at least in trabecular BMUs in rabbits treated for up to 414 days. Bone mineral density (BMD) increased similarly in the two treatment groups.

When one drug suppresses remodeling intensity 'more' than another, as widely held for alendronate over risedronate (8), it is implicit that there is less continued remodeling during alendronate than risedronate treatment. The net rise in BMD when a bisphosphonate is commenced is the result of filling of (i) existing cavities at the time of treatment (which should be the same if baseline remodeling intensity is the same in each group), (ii) concurrent secondary mineralization of osteons formed weeks to months before that now are not removed because of the reduced remodeling intensity, and (iii) the number of new cavities appearing during treatment (9). If alendronate suppressed remodeling more than risedronate then the rise in BMD should be higher than with risedronate. This was not observed in the study by Fuchs *et al.* (1).

One of the factors determining a drug's remodeling suppressant 'potency' is how well it is distributed within bone to be absorbed on the intracortical, endocortical, and trabecular surfaces upon which remodeling (signaled within matrix by microdamage, apoptotic osteocytes or other factors) is initiated. Alendronate is more tightly bound to matrix and so penetrates matrix less than risedronate (10). Risedronate penetrates matrix more and so may reach more remodeling foci and suppress remodeling sooner than alendronate. Allen *et al.* provide evidence of this (2). If remodeling is suppressed sooner and perhaps more greatly with risedronate than alendronate, why didn't BMD also rise sooner and more greatly with risedronate than alendronate?

The surface/volume ratio of trabecular bone, the subject of the paper by Fuchs *et al.* (1), is large and so access to this surface or the mineralized matrix beneath may not be a limiting factor influencing remodeling suppressant potency. However, data concerning cortical bone, a structure with a low surface/volume ratio, was not the subject of this manuscript. The observations may differ in cortical bone; remodeling initiated upon surfaces of the haversian canals traversing cortical bone may be less accessible to being inhibited by bisphosphonates, particularly those that are tightly bound to mineral and so do not penetrate deep into matrix surrounding the haversian canals (10).

Denosumab, the humanized antibody to RANKL, reduces the production of osteoclasts and the activity and lifespan of existing osteoclasts (11). It is not bound to bone surfaces so it may have greater accessibility to remodeling sites initiated within matrix. This may contribute to the more rapid and greater suppression of remodeling and the greater increase in bone density in human subjects particularly at the distal radius where alendronate slows bone loss but does not increase BMD (12). A greater reduction in intracortical porosity is reported in studies in animals than observed with alendronate (13). Whether the greater suppression of remodeling results in a greater increase in tissue mineralization density with denosumab than alendronate (as osteons undergo more complete secondary mineralization rather than being removed) remains to be determined. Understanding the morphological changes accompanying antiresorptive therapy requires consideration of both the extent of remodeling suppression by site and the residual remodeling that continues despite treatment.

The work published by Eastell *et al.* raises several other questions (3). In this 12-month study of 285 postmenopausal women comparing different dose regimens of the cathepsin K inhibitor ONO-5334 and alendronate, BMD increased at the lumbar spine and proximal femur. The question is, why? The increase in BMD following

antiresorptives like bisphosphonates or denosumab is the result of perturbation of steady state—pre-treatment resorption sites refill, reducing the size of the remodeling transient; porosity decreases and osteons undergo primary and more complete secondary mineralization. This early rapid increase in BMD is directly the result of this perturbation—filling of the many resorption sites excavated prior to treatment (reducing the remodeling space deficit) offset by the concurrent appearance of fewer new resorption sites (expanding the remodeling space deficit).

Cathepsin K inhibitors do not appear to reduce remodeling intensity (14). If this is correct then there is no perturbation of steady state remodeling—it remains at its pre-treatment intensity. How then does BMD increase? One possibility is that filling of resorption cavities present at the start of treatment proceeds with the appearance of the *same* number of new, but now more shallow resorption sites. The net effect may be a modest rise in BMD; this is likely to be modest because a reduction in the negative balance, if it occurred, will be small compared to the reduction in resorption produced but reducing activation frequency or the numbers of remodeling sites appearing upon the endosteal envelope. Whatever this rise, if the resorption sites are more shallow and the volume of bone formed in each is the same, then the negative BMU balance may be reduced. This will slow bone loss but not increase BMD. If the BMU balance becomes positive then it is advantageous to keep bone remodeling high because each remodeling event will deposit a positive amount of bone upon the bone surface. Data are needed. If remodeling continues at the same intensity but with more shallow resorption cavities then, in the longer-term, secondary mineralization may not rise as much as it does with agents that suppress remodeling intensity. Again, data are needed.

There was little or no suppression of bone formation markers compared with alendronate, although the suppressive effects on bone resorption markers were similar. Interpretation of this information is

difficult. Circulating remodeling markers are called 'resorption' or 'formation' markers but both reflect the surface extent of remodeling upon the endocortical, trabecular and intracortical components of bone's inner (endosteal) surface. Suppression of 'resorption' markers but not 'formation' markers does not necessarily mean there is a dissociation at the cellular level resulting in a reduction in the volume of bone resorbed by each BMU and continued formation of the same volume or a larger volume of bone by that BMU. There is no evidence that the balance of these markers is a surrogate of bone balance between the volumes of bone resorbed and formed by each BMU remodeling bone. One other possibility is that these agents are anabolic. Some evidence suggests that periosteal apposition is increased using balicatib in monkeys (15). Here too data are needed.

The fourth paper to appear has another lesson. Fitzpatrick *et al.* (4) report that ronacaleret, a calcium receptor antagonist, increased BMD at the lumbar spine but resulted in bone loss at the axial skeleton. The rationale underlying the development of this class of drugs is based on the notion that an increase in endogenous parathyroid hormone might have an anabolic effect on the skeleton. It did not; BMD decreased at the appendicular skeleton suggesting the net effect was not anabolic but in the presence of osteoclastic activity endogenous PTH increased bone resorption.

Thus therapeutic agents influence bone structure and strength by influencing tissue level and cell (BMU) level remodeling. Most antiresorptives, like the bisphosphonates, perturb the intensity of remodeling—shifting it from a higher to a lower steady state by reducing the intensity of remodeling, reducing the depth of resorption of the remodeling sites or both. The changes in the material composition and structure of bone will vary according to the degree of suppression of remodeling, the residual remodeling, the reduction in resorption pit depth and how much bone is deposited in the more shallow resorption pit. Defining these changes is a challenge. BMD does not

capture the net effect of filling of resorptive cavities (reducing porosity), the appearance of fewer new resorptive cavities that increase secondary mineralization of osteons no longer removed, while the residual remodeling increases porosity while replacing older, more mineralized osteons with new, less densely mineralized osteons (reducing tissue mineralization density). Residual remodeling during treatment reflects the potency of the drug in suppressing remodeling and part of this appears to be its accessibility to sites undergoing remodeling.

**Conflict of Interest:** Dr. Seeman reports that he is an advisory board member for Amgen, Eli Lilly, MSD, Novartis, Sanofi-aventis, Servier, and Warner Chilcott, and that he has participated in symposia at national and international congresses for several of these companies.

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