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PERSPECTIVES

Anabolic Plus Antiresorptive: Is One Plus One More or Less Two?

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Abstract

The anabolic effect of parathyroid hormone (PTH) 1-34 is remodeling- and modeling-based. Prior or concurrent use of remodeling suppressants may blunt the rise in remodeling markers and bone mineral density (BMD) produced by PTH1-34, perhaps because 70% of the anabolic effect of PTH1-34 is remodeling-based. Cosman *et al*. report the opposite; PTH1-34 plus zoledronic acid (ZA) initially produced a greater increase in BMD than PTH1-34 alone. While this may be the result of the modeling-based anabolic effect of PTH1-34 (which is not suppressed by ZA), it is unlikely to be the only explanation as modeling-based bone formation probably also occurs when blunting is reported with other combined antiresorptive-anabolic regimens. A more likely explanation is that ZA produces potent remodeling suppression in the first month of parenteral administration which suppresses the appearance of new resorptive cavities allowing refilling of the many resorption cavities present prior to treatment. Whilst evidence is lacking, the net effect is probably a reduction in intracortical porosity and more complete secondary mineralization of osteons that would otherwise have been replaced with less densely mineralized young osteons. In addition, deposition of new under-mineralized bone in the PTH1-34 alone group may decrease or leave BMD unchanged. While evidence for these morphological changes is needed, changes in BMD account for little of the variance in anti-fracture efficacy between treatments, so the use of a greater increase in BMD as a surrogate of better antifracture efficacy is questionable. *IBMS BoneKEy*. 2011 May;8(5):221-228.

Most, but not all, studies suggest that the effects of PTH1-34 or 1-84 on bone remodeling markers and bone mineral density (BMD) are blunted by prior or concurrent administration of a potent bisphosphonate (1-7). Cosman *et al*. report the opposite; zoledronic acid (ZA) plus PTH1-34 increased BMD more than PTH alone, at least during the first months of therapy (8). These disparate findings can be understood by examining the independent and interacting effects of each drug on the material composition and structure of bone.

Antiresorptives Increase BMD by Perturbing Steady State Remodeling

A potent remodeling suppressant like ZA suppresses remodeling by 80% within the first 1 to 3 months of administration, at least as measured using bone remodeling markers (9;10). When ZA is started, remodeling is perturbed; BMUs initiated just prior to treatment complete remodeling by bone formation but with the concurrent appearance of only 20% of the pre-treatment remodeling units beginning their resorptive phase. The net result is more bone is deposited upon the internal surfaces than is being removed producing the early rapid increase in BMD proportional to the remodeling intensity present when treatment was started.

The increase in BMD is the net result of: (i) primary and beginnings of secondary mineralization of osteoid deposited in resorption cavities (cutting cones in cortical bone, trenches upon endocortical and trabecular surfaces), (ii) the appearance of ~20% of the pre-treatment BMUs which excavate bone with its mineral content, and (iii) more complete secondary mineralization of osteons and hemiosteons formed months earlier that otherwise may have been remodeled and replaced by younger, less densely mineralized bone. The almost complete refilling of resorption cavities is

likely to reduce intracortical porosity and stress concentrators on trabeculae (11). The rise in secondary mineralization increases tissue stiffness (12).

Antiresorptives, as implied by their name, should at best *maintain* BMD if remodeling is abolished, or diminish the decline in BMD if remodeling continues, but they *increase* BMD. They do this by reducing the size of the transient remodeling space deficit. The rise in BMD is a consequence of shifting remodeling from a higher to lower level which contracts the remodeling space deficit that exists because excavated cavities are not instantaneously refilled by bone formation; there is a delay in initiation of formation (the reversal phase) and then formation proceeds slowly to completion by cells of the BMU.

In morphological terms, the remodeling space deficit or remodeling transient comprises the resorption cavities – the voids (porosity, trenches), osteoid that has not been mineralized, bone that has undergone primary but incomplete secondary mineralization, and earlier formed osteons and hemiosteons that have not undergone complete secondary mineralization (13). The increase in bone tissue volume (filled intracortical canals, trenches upon trabecular and the endocortical surface) and the greater completeness of primary and secondary mineralization of this bone volume producing the increase in BMD do not change the dimensions of the bone; periosteal, endocortical or trabecular perimeters remain unchanged (but intracortical pores may decrease); this increase in BMD is not an anabolic effect, it is the result of contraction of the remodeling space deficit produced by refilling of the excavated cavities and a reduction in numbers of remodeling units. The greater the number of sites, the greater the transient remodeling space deficit and the greater the rise in BMD in response to antiresorptive therapy. Whether antiresorptives reduce the negative BMU balance by altering the work or life-span of the cells of the BMU *in vivo* is less clear (14).

Restoration of Remodeling at a Slower Remodeling Intensity: Good and Bad

Later changes in BMD in response to antiresorptives have a different morphological basis and biomechanical consequences. After ~3 months of treatment with ZA, steady state remodeling is restored but continues at 50% of its pre-treatment intensity during the ensuing 12 months or more, at least as determined by the level of suppression of remodeling markers (9;10). While the morphological effects of antiresorptive agents are mainly considered in terms of their potency in suppressing remodeling, the morphological changes are also the consequence of the continued remodeling that occurs during therapy. In the case of ZA, remodeling suppression is 50% and continued remodeling also occurs at ~50% of the pre-treatment remodeling intensity when steady state is restored (9;10).

Provided BMU balance remains negative, continued remodeling progressively decreases total matrix volume producing structural decay. On the other hand, remodeling suppression slows structural decay but allows more complete secondary mineralization of the slowly diminishing bone matrix volume. As the total matrix volume that is undergoing more complete secondary mineralization is greater than any loss of matrix with its mineral produced by continued slow remodeling, BMD will continue to increase. However, material and structural strength may decline due to slow structural decay, increasing homogeneity of tissue mineral density distribution, and collagen cross-linking by advanced glycation end products (15). BMD will continue to rise until secondary mineralization of all osteons comprising the diminishing total bone matrix volume is complete. It may then start to decrease as continued remodeling removes matrix volume with its mineral content.

So, BMD may continue to increase, remain stable or decline depending on the completeness of secondary mineralization, the residual intensity of the suppressed remodeling and the size of the negative BMU balance in an individual. Whatever the net change in BMD or lack of change in

BMD, bone strength cannot be determined by measuring change alone, in BMD or any property of bone, as done in many studies, including the work by Cosman *et al*. (8). Baseline morphology must also be quantified.

For example, if baseline tissue mineral density is low, any increase is likely to increase material stiffness. If it is high, further increase may reduce toughness; both scenarios will produce a rise in BMD. If baseline structural decay is severe with high porosity and loss of trabecular connectivity, remodeling suppression may reduce porosity, increase tissue mineral density and BMD, but bone strength may not improve in the face of so much damage. If baseline structure is severely compromised and baseline remodeling is low and is further suppressed, BMD may rise but compromising material strength may be sufficient to contribute to atypical fractures. This heterogeneity in material composition and structure, the differing net effects of porosity and secondary mineralization on BMD are outside the grasp of bone densitometry and may partly explain why BMD lacks sensitivity and specificity for fracture prediction or the assessment of the effects of treatment on bone strength (16).

What Happens When PTH1-34 or 1-84 and ZA Are Co-administered?

The anabolic effect of PTH1-34 is modeling- and remodeling-based (17;18). Modeling-based bone formation is identified by the deposition of new bone upon smooth surfaces. Remodeling-based bone formation is identified by the deposition of new bone upon crenated surfaces. Bone formation also occurs by 'spillover' from a remodeled region onto an adjacent quiescent surface following PTH1-34 (18), and under normal remodeling circumstances (19).

Most of the bone's inner (endosteal) surface is quiescent while only 10-15% of the surface displays remodeling activity (20). Even though this much larger quiescent surface provides a bountiful area upon which modeling-based bone formation can reconstruct the skeleton, it appears that 70% of all the newly deposited bone produced by PTH1-34 arises from remodeling-based bone formation upon the smaller surface area (17). Indeed, the higher the baseline remodeling, the greater the rise in BMD in response to PTH1-34 (21;22). This rise is not blunted by weak remodeling suppressants like raloxifene (23), and appears to be less blunted by risedronate than by alendronate (24), perhaps because risedronate has a lower binding affinity to hydroxyapatite (25); the evidence that alendronate suppresses remodeling more than risedronate is not compelling (26). Thus, the dependence of most of the anabolic response to PTH molecules on the available remodeling surface area and remodeling intensity provides a seemingly satisfactory explanation for the blunting of rise in remodeling markers and BMD following PTH1-34 or 1-84 with a potent remodeling suppressant like alendronate in some studies (1-4).

Why then did Cosman *et al*. find a greater effect of PTH1-34 plus ZA over that observed with PTH1-34 alone, at least initially (8)? One explanation may be that the modeling effect of PTH1-34 proceeded despite ZA. While modeling-based bone formation accounts for only 30% of the total anabolic effect of PTH molecules, when combined with the potent (80%) early remodeling suppression with ZA, the *net* rise in BMD so produced may be greater than achieved using PTH1-34 alone, particularly as PTH1-34 alone may initially reduce BMD (see below). Whilst evidence is lacking, the morphological basis underlying the rise in BMD is predicted to be: (i) new bone formation on quiescent surfaces produced by PTH1-34, (ii) a reduction in intracortical porosity, and (iii) continued secondary tissue mineralization produced by potent suppression of remodeling by parenteral administration of ZA.

The greater BMD response to combined therapy than to PTH1-34 alone is also likely to be the result of PTH1-34 alone increasing remodeling intensity which may result in a transitory rise in intracortical porosity lowering cortical density (25;26). Moreover, the newly deposited bone by the BMU will have a lower tissue density, and any modeling- or remodeling-based newly

deposited bone will also be under-mineralized. Thus, BMD may not rise, or may decrease with PTH1-34 alone (2). Porosity will decrease relative to baseline in the combined group because of the likely effect of ZA in reducing porosity as discussed above, and it will not increase with PTH1-34 because of inhibition of PTH1-34-mediated remodeling by ZA. Porosity will be lower relative to the PTH1-34 alone group because of these two mechanisms plus the transitory rise in porosity in the PTH1-34 alone group.

If this interpretation is correct, why doesn't the modeling-dependent anabolic effect of PTH1-34 or 1-84 plus alendronate also produce a higher BMD than PTH1-34 or 1-84 alone (1-4)? Oral alendronate suppresses remodeling less than an intravenous bolus of ZA, at least initially (9;10). As occurs in later stages of ZA treatment, continued remodeling at 50% of the pretreatment rate as determined by remodeling markers produces intracortical porosity, structural decay and replacement of osteons with younger osteons while remodeling suppression by 50% of the pretreatment rate allows secondary mineralization of osteons formed previously. These opposing effects may explain why *net* cortical vBMD does not increase during alendronate treatment (27-29).

Thus, the overall net effect of the modest modeling-dependent anabolic effect of PTH1-34 or 1-84 plus continued remodeling may account for 'blunting' in BMD response when alendronate and PTH are co-administered. It may also explain the findings in the second six months of the study by Cosman *et al*.; the rise in BMD at the spine and femoral neck was *less* with combined PTH1-34 plus ZA than with PTH1-34 alone (8). At this later stage, steady state remodeling is restored with equal numbers of BMUs completing remodeling and new ones initiating their resorption phase but at 50% instead of 80% of pre-treatment remodeling intensity. Remodeling may have increased enough to eroded bone offsetting any modeling-dependent anabolic effects produced by PTH1-34.

BMD Was a Good Beginning, but Not in All Respects

No adequately powered comparator trials with fracture outcomes address whether combined antiresorptive plus anabolic therapy reduces fracture rates more greatly than either regimen alone. Many trials compare changes in BMD in response to one antiresorptive versus another, an antiresorptive versus an anabolic agent or single versus combined regimens, presumably under the assumption that a greater increment in BMD with one regimen over another means that greater antifracture efficacy may be inferred.

While this seemed like a good idea at the time, it has not withstood the test of time; a change in BMD accounts for only 10-30% of the fracture risk reduction in clinical trials. Even patients losing bone during treatment benefit from a fracture risk reduction (16). Differences in baseline remodeling (which determine the size of the reversible remodeling space transient) are critical determinants of the BMD response to an antiresorptive (16). BMD is neither a sensitive nor specific surrogate of antifracture efficacy, and a difference in increment in BMD of a few percentage points between any two regimens, whether they are single or combined, is difficult to interpret for many reasons (30;31).

In the context of this discussion, the BMD measurement cannot distinguish changes in material composition and structure which may move in opposite directions (tissue density rising due to remodeling suppression, porosity increasing due to continued residual remodeling) with a single therapy or combined therapy. The BMD measurement is also blind to changes upon the periosteal, intracortical and trabecular surfaces responsible for changes in microarchitecture and thus, bone strength. So, whatever the effect on BMD – blunting, no change or a greater change in BMD – BMD cannot be relied upon to signal corresponding blunting, no change or greater increase in bone strength.

Dynamic histomorphometry is needed to confirm whether there is modeling-based

bone formation, whether remodeling is suppressed, intracortical porosity is reduced and tissue mineral density is increased with the combination of PTH1-34 plus ZA and not so, or less so, with PTH1-34 plus alendronate. These effects needed to be assessed early, when steady state remodeling is perturbed, and later, when steady state remodeling is restored at a lower intensity. Inferences regarding differences in effects produced by differences in the mode of administration require comparing parenteral and oral preparations of the *same* drug, while inferences regarding the effects of different drugs require studies comparing different drugs in the *same* study. These data are not available so that the veracity of the views expressed here remain untested.

Does one plus one add up to more or less two is asking the wrong question. It doesn't matter. A change in BMD provides little, if any, insight into the effects of combined therapy on the material composition and structure of bone over single therapy. Nor does it provide insight regarding potentially superior antifracture efficacy over single therapy. Therefore, what is the justification for studies comparing BMD change between regimens?

Choosing therapy and assessing whether it is successful or unsuccessful depend on defining the pathogenesis, material and structural basis of the fragility at baseline, and quantifying the changes produced in each; measuring BMD is not a solution. Antifracture efficacy is ~50% for vertebral fracture, ~40% for hip fractures and ~20% in the few trials reporting any benefit against nonvertebral fractures (32), the latter accounting for ~80% of all fractures (33).

This low antifracture efficacy may have more to do with how we select patients and monitor treatment than with the therapeutic agents available. Patients with a 'minimal trauma' fracture or a fall 'from no greater than the standing position' are not all the same. There is a great deal of heterogeneity in the pathogenesis, material and structural basis of bone fragility from person to person (31). We have entered an era where material composition and structure can be measured noninvasively *in vivo*; let's go there.

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