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COMMENTARY

Dissociation between antiresorptive effects at endosteal surfaces vs bone-forming effects on cortical (periosteal) surfaces

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Commentary on: Cusick T, Chen CM, Pennypacker BL, Pickarski M, Kimmel D, Scott BB, Duong LT. Odanacatib treatment increases hip bone mass and cortical thickness by preserving endocortical bone formation and stimulating periosteal bone formation in the ovariectomized adult rhesus monkey. J Bone Miner Res 2012;**27**:524–537; Masarachia PJ, Pennypacker BL, Pickarski M, Scott KR, Wesolowski GA, Smith SY, Samadfam R, Goetzmann JE, Scott BB, Kimmel DB and Duong LT. Odanacatib reduces bone turnover and increases bone mass in the lumbar spine of skeletally mature ovariectomized rhesus monkeys. J Bone Miner Res 2012;**27**:509–523.

Bisphosphonates (BPs) were the first class of drugs developed for the treatment of postmenopausal osteoporosis.[1] They reduce bone resorption by inhibiting the function of osteoclasts, and in the process they inhibit bone remodeling, both resorption and formation, as they are tightly coupled. BPs exhibit strong reduction in fracture risk,[1–3] because they inhibit excessive remodeling that is the principal factor in the pathogenesis of osteoporosis and resultant low-trauma fracture.[4]

A new 'antiresorptive' agent is now under development[5,6] with information available from preclinical research studies[7] and from early dose-ranging human trials.[8] Cathepsin K (CatK) is a cysteine protease, abundant in osteoclasts, active under acidic conditions, and the principal enzyme that degrades type 1 collagen.[5] Odanacatib (ODN) is a selective, potent, orally bioavailable CatK inhibitor. The antiresorptive drugs in current use, principally the BPs, decrease osteoclast activity and numbers. ODN, on the other hand, preserves osteoclast viability, cellular activity and acid production, while selectively inhibiting the removal of matrix protein. It was developed as an agent that would correct the imbalance between bone resorption and formation.

However, preclinical and early human clinical experience has uncovered surprises.[7–11] Preclinical studies[7,9,10] demonstrated continued bone formation during treatment with ODN in ovariectomized animal models of bone loss (rabbit and non-human primate (NHP)). An early human trial[8] exhibited significant, dose–response gains in bone mineral density (BMD, DXA) in the lumbar spine, total hip and femoral neck, but no significant gain in the distal 1/3 radius. Surprisingly, bone histomorphometry of iliac crest biopsies in this study showed minimal suppression of trabecular bone formation as measured by mineralizing surface, mineral apposition rate or activation frequency, and all specimens exhibited fluorochrome double label. These findings are significantly different than found in BP-treated patients where iliac biopsies demonstrate that bone remodeling is suppressed in all specimens, and in a minority, it is suppressed to the extent that the biopsies do not exhibit fluorochrome label at all.[12,13]

Recent NHP studies,[9,10] the objects of this commentary, showed gains in bone mass of the spine and hip, and demonstrated some important insights. Lumbar spine increases in bone mineral content and BMD[9] were accompanied by proportionate increases in mechanical strength testing, not a surprise. However, vertebral dynamic histomorphometry showed continued bone formation on trabecular and endocortical surfaces at nearly the same rate as controls. This was a bit of a surprise. Vertebral body periosteal bone formation was not reported.

The hip studies in the same animals yielded interesting and more surprising findings. There were striking, dose-dependent increases in hip and femoral neck BMD at 21 months of treatment, 19% and 24%, respectively, in the high dose group ($30\,mg\,kg^{-1}$). The data also showed striking increases in cortical thickness, particularly at the femoral neck. The histomorphometry of the femoral neck and proximal femur showed that this resulted from maintenance of endocortical formation coupled with marked increases in periosteal new bone formation.[10]

Bone remodeling markers[9] showed minimally reduced levels of formation and resorption markers at the high dose, and little or no change at the low dose. The circulating Trap-5b levels were not suppressed on treatment, and were actually a bit higher than those found in the intact animals, indicating that osteoclast numbers were not suppressed. This was concordant with the measurements of osteoclast numbers in the histomorphometry.

In summary, the animal data showed evidence of marked regional increases in BMD at the femoral neck and proximal femur. The vertebral bodies showed restoration of BMD to levels found in the intact animals, and about 15% above the ovariectomized animals given vehicle. Taken together, these data suggest that ODN results in increased sensitivity to normal loading, as the regional increases in BMD were in areas of the skeleton that would be expected to be loaded more than other areas in these caged NHPs (Rhesus monkeys). In all locations, histomorphometry showed maintenance of mineral apposition rates. The combined data for the femoral neck and proximal femur show a morphologic pattern of new bone formation consistent with adaptation to loading.

How to explain?

Previous ODN data showed that the osteoclasts exhibited abortive resorption, and stained collagen particles appeared in the cytoplasm of osteoclasts.[14] Also (though not reported in the manuscript[8]), resorptive surfaces in the transiliac biopsies in the human study showed what appeared to be shallow, but nonetheless, clearly present scalloping. An attractive hypothesis of its action would be that there is enough resorption of the collagen matrix that a small amount of non-collagen signaling molecules are liberated.[15] Further, these molecules could then signal the load-adaptive machinery (Wnt/Lrp5/β-catenin) making it more sensitive to loading.[16–18] Thus, this model would suggest that in skeletal areas where loading occurs that causes mechanical strain above the new lower threshold for adaptation, an anabolic effect takes place. The location of the regional anabolic appearance, that is, in the femoral neck and proximal femur, does seem to be in areas where more loading is taking place in these caged animals. It is difficult to imagine how else an anabolic effect would appear in a regional distribution in the presence of a pharmacologic agent administered systemically.

Indeed, the ideal bone anabolic agent would likely be one that works by increasing the skeleton's sensitivity to load adaptation, because that mechanism would tend to avoid problems from creating new bone in areas that would be dangerous, such as in the spinal column (spinal stenosis) or nerve root foramina. The description of the high bone mass kindred[19] illustrates an example of increased sensitivity to loading. In that kindred, the increased bone mass was distributed preferentially in areas where greatest load/strain occurs (axial BMD >upper extremity BMD), and the increase in BMD (*T*-scores of +5.0) resulted in a phenotype with regional differences concordant with regions of increased load. The fact that the bones in the kindred were of completely normal shape lends credence to that hypothesis, as loading normally has a strong role in the accrual of bone mass and shape during growth and development.[20] Subsequent *in vivo* transgenic rodent experiments demonstrated increased bone formation in response to given load-induced strains compared with normal littermates, all of which would be expected if there was increased sensitivity to strains from mechanical loads.[16]

In summary, the increase in bone mass from administration of ODN to ovariectomized NHPs in the papers by Cusick *et al.*[9] and Masarachia *et al.*[10] could be the result of several factors; a small increase in bone mass as a result of filling of the remodeling space, a halt in the micro-structural deterioration by reducing the excess remodeling and, finally, most importantly, a significant regional anabolic effect corresponding to the skeletal areas undergoing the most loading. In contrast, the pivotal human studies of BPs showed that reduction in remodeling was generalized, as were increases in BMD.

It should be noted that increased sensitivity to loading remains a hypothesis to explain the action of ODN. There has not yet been a direct test of this hypothesis. Unfortunately, species specificity prevents testing it in rodents because ODN is not functional in that model, the most convenient animal for testing the response to controlled loading *in vivo*. Perhaps a CatK inhibitor can become available for rodent studies, or studies in another animal model, to test the hypothesis.

The studies by Cusick *et al.* and Masarachia *et al.* were done in primates. There has been study in humans[8] and the results are congruent with these primate data in that bone formation rates are sustained while resorption is decreased and BMD increases. Further study is needed to understand the mechanism of action of ODN.

Conflict of Interest

Robert R Recker, MD, MACP, FACP, is a paid consultant for Merck, Lilly, Pfizer, Procter & Gamble, Amgen, Roche, Glaxo Smith Kline and Novartis; and has received grant/research support from Merck, Lilly, Wyeth, Procter & Gamble, Amgen, Roche, Glaxo Smith Kline, Novartis and Sanofi-Aventis through grants to his institution.

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