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COMMENTARIES

Current, New and Emerging Anti-Resorptive Drugs; Antibody Blockade Of RANKL Action

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Commentary on: McClung MR, Lewicki EM, Cohen SB, Bolognese MA, Woodson GC, Moffett AH, Peacock M, Miller PD, Lederman SN, Chesnut CH, Lain D, Kivitz AJ, Holloway DL, Zhang C, Peterson MC, Bekker PJ, AMG 162 Bone Loss Study Group. Denosumab in postmenopausal women with low bone mineral density. *N Eng J Med*. 2006 Feb 23;354(8):821-31.

The common factor mediating osteoclast formation in response to all known stimuli is nuclear factor-κB ligand (RANKL) (1) that binds to its receptor, RANK, on hemopoietic precursors to promote osteoclast differentiation, as well as osteoclast survival and activity. The decoy receptor, osteoprotegerin (OPG), is an essential paracrine regulator of osteoclast formation, produced by the osteoblasts and binding RANKL to limit its promotion of osteoclast formation through its receptor, RANK. Studies in genetically altered mice have established clearly the essential physiological roles of these TNF ligand and receptor family members in controlling osteoclast formation and activity. Thus, regulated production of RANKL and of its local "brake" mechanism, OPG, are essential for maintenance of normal bone turnover. These discoveries revealed a pathway that was obviously rich in targets for pharmaceutical development, many of which have been explored in the last few years in preclinical and some early clinical studies. For example, recombinant OPG was effective in preventing the bone loss of estrogen lack, and the increased resorption associated with bone metastases, humoral hypercalcemia of cancer, and adjuvant-induced arthritis (2;3). Formation of significant antibody titers in a patient given OPG brought that development to an end. Other routes to anti-resorptive drug development in this pathway that continue to be explored include small molecule compounds that inhibit RANK signaling, or that promote production of OPG (4). The first moderately large clinical study (5) has been carried out with a fully humanized monoclonal antibody against RANKL (denosumab, known in earlier development work as AMG 162).

In this 12-month study in 412 postmenopausal women with low bone mineral density (5), several doses of denosumab were injected at either 3- or 6-month intervals and compared with open-label oral alendronate administered once weekly. Significant increases in BMD in response to both injection schedules of denosumab were found at the lumbar spine and hip, with the magnitude of these changes being approximately the same as those with alendronate. Denosumab treatment was followed by a very rapid decrease in levels of bone resorption markers. Most remarkable was the prolonged suppression of these markers, with the higher doses of denosumab 3-monthly achieving and maintaining very low resorption markers. As we have come to expect from effective anti-resorptive treatments because of the coupling of bone formation to resorption (6), markers of bone formation also decreased.

As a proof of concept that substantial bone resorption inhibition can be achieved by neutralizing RANKL, this was a successful

study. The exceptionally prolonged and powerful action of this fully humanized antibody is a striking property that reflects a previous phase 1 study showing very prolonged action after injection (7). In one sense, the very prolonged effect is an advantage, providing a prospect of treating by subcutaneous injection every few months and thereby facilitating compliance. On the other hand, there is no reason to suppose that simply achieving an ever-greater inhibition of resorption will improve fracture reduction or make for better bone. Do we want profound, prolonged suppression of bone turnover, or should we be less heavy-handed?

Comparison with Existing Treatments, Particularly Bisphosphonates

In the last ten years, several bisphosphonates and the selective estrogen receptor modulator (SERM), raloxifene, have been shown in careful, thorough clinical trials to reduce fracture incidence in osteoporosis by 30-50% (8). This is the starting point. Although it might reasonably be asked whether we need further anti-resorptives, the real and potential limitations of existing therapies are sufficient to warrant the continued search for new approaches. The aims would be to improve the fracture risk reduction if possible, to avoid the possibility of long-term effects on bone structure, to find drugs whose effects reverse with cessation of therapy, and drugs that inhibit resorption without inhibiting bone formation.

The affinity of bisphosphonates for bone and their great stability ensures their prolonged storage in bone, and contributes to their long-lasting suppressive effects on bone remodeling. This has become more evident with the steadily increasing potency of these compounds. Blockade of RANKL activity by denosumab is remarkably effective and prolonged in its suppression of indices of bone resorption, so it needs to be viewed as in the same class as bisphosphonates, although obviously with a very different mechanism. The resorptive phase of the bone remodeling cycle removes damaged bone, and therefore prolonged suppression of remodeling could possibly do harm (9). Micro-damage and increased bone brittleness occurs in animals given high doses of bisphosphonates, but these doses are well above those used clinically, and convincing evidence of a deleterious effect in humans is lacking, even though there are uncontrolled case reports of impaired fracture healing with alendronate (10). Furthermore, the association of some bisphosphonates with occurrence of osteonecrosis of the jaw (11) could be related to excessive suppression of bone remodeling. It remains to be established whether drugs that greatly suppress remodeling are more appropriate in persons with high remodeling and low tissue mineral density, but deleterious in persons with lower remodeling and normal tissue mineral density (in whom further suppression may predispose to micro-damage) (9).

As has been the case with bisphosphonates, resorption inhibition by anti-RANKL treatment in the 12-month study was accompanied by suppression of marker indices of bone formation. Although this needs to be confirmed in a longer study, it is most likely to be a feature of denosumab action, and reflects the coupling of formation to resorption. In seeking new anti-resorptive drugs, would it be possible to achieve a required effect on resorption without inhibiting bone formation – in other words, uncoupling bone formation from resorption? Some experimental and preclinical evidence suggests that there might be a prospect of doing so.

Are There Other Ways to Proceed?

Many examples continue to emerge that illustrate the coupling concept, with bone formation increasing or decreasing when bone resorption changes in the same direction. Examples include *OPG*(-/-) mice, in which increased bone formation accompanies their increased osteoclastogenesis and resorption (12), and mice with selectively inactivated gp130-signaling pathway (13). Mice lacking *c-fos,* which fail to generate osteoclasts, have reduced bone formation and resorption (14),

but on the other hand, in mice deficient for either *c-Src* (15) or the chloride-7 channel (*ClC-7*) (16), bone resorption is inhibited without any inhibition of the rate or extent of formation. In each of these mouse mutations, osteoclast numbers are maintained, but the osteoclasts are unable to resorb bone. This is the case also in human subjects with inactivating mutations either of *ClC-7* (17) or the vacuolar H^+ATPase (18). A possibility is that osteoclasts are able to generate a factor (or factors) that can contribute to bone formation, despite the fact that they do not resorb bone (19). Early data with an orally delivered CLCN7 inhibitor showed that it inhibited bone loss in the ovariectomized rat without inhibiting bone formation (16). It is possible that such inhibitors of resorption could be more readily combined with anabolic therapy than those resorption inhibitors (*e.g.* bisphosphonates, and likely anti-RANKL) that lead to inhibited bone formation.

Thus, although effective inhibitors of osteoclast activity are currently known and in clinical use, additional ones are being developed and will be used if they are better suited for particular indications or provide greater efficacy, safety or convenience. The aim of resorption inhibitors is to reduce fracture incidence safely. There is probably a limit to the safe reduction in fracture risk that can be achieved in this way, and it remains to be seen whether that limit can be reached simply by effecting more powerful inhibition of bone resorption. Maybe a new class of resorption inhibitors, one that does not inevitably reduce bone formation, will be appealing.

The neutralization of RANKL action certainly looks as though it will be an effective approach, and it brings much interest to the field. Other aspects of its physiology will be important to consider during its evaluation. RANKL production is widely distributed in tissues (20). Furthermore, while it is essential for normal osteoclast formation, activity and survival, it has an important role in lymphocyte development, with RANKL-null mice showing severe lymph node deficiencies and defective T and B cell development, in addition to osteopetrosis (21). As larger clinical trials of denosumab proceed, and especially if it comes to wider clinical use, no doubt these properties will be borne in mind as safety issues are addressed.

Conflict of Interest: The author reports that no conflict of interest exists.

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