Denosumab: Anti-RANKL Antibody

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Denosumab (anti-receptor activator of nuclear factor-κB ligand [RANKL] antibody) is a novel agent, a fully human monoclonal antibody that inhibits osteoclastic-mediated bone resorption by binding to osteoblast-produced RANKL. By reducing RANKL binding to the osteoclast receptor RANK, bone resorption and turnover decrease. In phase 2 dose-ranging studies, denosumab had a rapid onset and offset effect. Also, in patients who had received 2 years of denosumab and were discontinued for the third year, rechallenge with denosumab during the fourth year demonstrated a return of responsiveness to denosumab that mimicked the initial treatment. Phase 3 pivotal fracture data were recently presented with positive outcome data; denosumab (60 mg subcutaneously every 6 months) significantly reduced vertebral, nonvertebral, and hip fracture risk compared with placebo, and had an excellent safety profile through 3 years of use. Denosumab will offer a novel approach to managing postmenopausal osteoporosis, one that should be associated with a high adherence rate and global fracture risk reduction.

Introduction
Bone remodeling is an ongoing process in human bone biology that is necessary to repair microdamage and renew skeletal integrity and strength [1,2]. The process of bone remodeling in humans replaces the entire human skeleton every decade. Bone resorption is intimately coupled to bone formation and vice versa. This process is regulated by systemic and local regulators of bone cell activity [3–5]. Systemic regulators of osteoblast differentiation and activity include endogenous parathyroid hormone, vitamin D metabolites, the interleukins, prostaglandins, phosphatidins, and the steroid hormones (eg, gonadal [estrogen and testosterone] and cortisol). Local regulators of bone remodeling that determine osteoclast differentiation and activity are the receptor activator of nuclear factor-κB ligand (RANKL) and osteoprotegerin, peptides that emanate from osteoblasts. Osteoclast receptor RANK and RANKL binding lead to osteoclastogenesis. The decoy receptor to RANK, osteoprotegerin, binding to RANKL leads to a decrease in osteoclast activity because less RANKL is available to downregulate RANK. Inhibitors of RANKL (eg, anti-RANKL antibody) lead to a decrease in osteoclastogenesis and osteoclast activity, thus reducing bone resorption (Fig. 1) [6]. Regulation of bone remodeling also includes the dominant cell in bone, the osteocyte [7,8]. The osteocyte-derived phosphonatin fibroblast growth factor 23 and sclerostin also have direct and indirect effects on bone turnover [9,10]. Specifically, sclerostin downregulates the critical osteoblast regulator Wnt, and inhibition of sclerostin also leads to an increase in osteoclastogenesis and activity, as does a group of peptides that may modify osteoblast activity independent of Wnt (eg, these include DKK1, LRPs, and the bone morphometric proteins).

Osteocytes also respond to mechanical signals, which lead to alterations in periosteal bone formation and bone strength. Low-level mechanical signals are anabolic to bone via pathways that involve, in large part, the osteocyte mechanostat [7].

Also, a growing body of evidence suggests that fat cells (adipocytes) may have a regulatory role in bone remodeling. Marrow stem cells may be differentiated to osteoblast or adipocytes, and the direction of differentiation may be dependent on several pathways—especially the level of insulin-like growth factor–binding proteins [11,12].

Thus, although many local and systemic factors regulate osteoblast differentiation and activity, the final common pathway emanating from osteoblasts that regulates osteoclast activity is the RANKL–osteoprotegerin competitive binding and subsequent availability of RANKL to the osteoclast receptor RANK. Because pharmacologic agents alter bone resorption (antiresorptive) agents by altering osteoclast activity, this article focuses on how these agents affect bone turnover, bone strength, and reduce the risk for low trauma fractures.

Anti-RANKL Antibody
The first fully human monoclonal antibody to RANKL (denosumab) will offer another choice for managing post-
menopausal osteoporosis (PMO) (Fig. 1) [13,14,15,16].

The phase II clinical dose-ranging data, now extended for 4 years, shows that the planned registered dose (60 mg subcutaneously every 6 months) has a rapid onset of inhibition of bone turnover to a greater extent than (head-to-head) with alendronate (70 mg/wk). In addition to this reduction of bone turnover, an effect on bone mineral density (BMD) dissipates rapidly after denosumab's discontinuation, while reintroduction of denosumab results in a return of the BMD and bone turnover marker (BTM) responsiveness when restarted (Fig. 2, Fig. 3) [16]. Also, the BTM and BMD response to restarting denosumab after 1 year of discontinuation of denosumab mimics the BMD and BTM response seen in treatment-naive patients (Fig. 2, Fig. 3). Thus, it would appear that there is no blunting of the BMD or BTM effect when denosumab is restarted.

Another very interesting observation in the long-term phase II denosumab data is that during the discontinuation (third year) of denosumab after 2 years of prior denosumab treatment, serum C-terminal collagen crosslinked peptide and bone-specific alkaline phosphatase not only increased back to baseline but rose above baseline ("overshoot"). In addition, despite continual discontinuation of denosumab for a second year after 2 years of denosumab treatment, all of the BTMs spontaneously returned back to baseline during the fourth year, even though no additional denosumab therapy was applied (Fig. 4). The same return back to baseline despite no additional therapy was also seen with the BMD measurements (figure not shown). The basic bone mechanism leading to the overshoot and return of BTMs and BMD back to baseline is unknown. There are theories that bone tissue is responding as a mechanostat in these scenarios and readjusting its level of turnover as a function of the mechanostat regulation of bone [17]. Because denosumab's pharmacokinetics differs from those of bisphosphonates in many ways, including the absence of bone retention for denosumab, it is entirely plausible that the readjustment in bone turnover and density seen after denosumab exposure then discontinuation is unrelated to the drug. A mechanostat hypothesis is highly likely to provide at least some of the answers.

In the phase II denosumab publications, there also was an increase in forearm BMD with denosumab administration, whereas the forearm BMD declined in the placebo and the alendronate groups. Forearm BMD also did not change or decline in the other registered bisphosphonate clinical trial data, as well as in the 1-34 and 1-84 parathyroid hormone trials. This unique property of denosumab is intriguing, and speculation exists that this increase in forearm BMD may suggest differential effects of denosumab on cortical bone and perhaps cortical bone strength. Preliminary data do show an increase in forearm and spine quantitative
Figure 2. Effect of denosumab retreatment on serum C-terminal collagen cross-linked peptide (CTX) (A) and bone-specific alkaline phosphatase (BSAP) (B) levels. Phase 2, 4-year clinical trial data showing the bone turnover marker response after discontinuation and then rechallenge to denosumab. Q3M—every 3 months; Q6M—every 6 months. (Adapted from Miller et al. [16•].)

Figure 3. Effect of denosumab retreatment on lumbar spine (A) and total hip (B) bone mineral density (BMD). Phase 2, 4-year clinical trial data showing the BMD response after discontinuation and then rechallenge to denosumab. Q6M—every 6 months. (Adapted from Miller et al. [16•].)

computerized tomography (QCT) at QCT measured cancellous and cortical bone forearm sites [18]. This denosumab effect on cortical bone, combined with the observations that denosumab increases the two-dimensional cross-sectional area of the hip, femoral neck, and femoral shaft as measured by the parameter hip structural analysis [19], provides evidence that denosumab increases cortical bone strength, consistent with the reduction in nonvertebral and hip fractures seen in the recent phase 3 denosumab fracture data.

Phase 3 Fracture Clinical Trial of Denosumab
The pivotal phase 3 data showing denosumab's beneficial effect on global bone strength were recently presented at the 2008 annual meeting of the American Society for Bone and Mineral Research [20•]. The FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months) trial randomized 7600 postmenopausal patients into two arms: placebo or denosumab (60 mg subcutaneously every 6 months). The primary end point
was a reduction in incident morphometric vertebral fracture over a 3-year period, whereas secondary end points were a reduction in hip and nonvertebral fractures and changes in BMD and BTMs. All designed end points were attained, and denosumab's effects were significantly better than placebo. A significant reduction was observed in vertebral (68%), nonvertebral (20%), and hip (40%) fractures seen with denosumab. As in the phase 2 clinical trial data, denosumab induced a significant increase in all BMD sites, including the forearm, a BMD response unique to denosumab and not seen with any other antiresorptive or anabolic agent registered for PGO.

Denosumab demonstrated an excellent safety profile in this large phase 3 clinical trial. No differences were observed in any adverse events or serious adverse events between placebo and denosumab. In particular, there were no cases of osteonecrosis of the jaw, infections, or neoplasms in the denosumab group.

Pharmacokinetics of Denosumab
The exciting and unique biological property of this fully human monoclonal antibody is that it will not reside in bone or be retained in bone, factors that have led to some of the unique and favorable (ability to offer "drug holidays") yet concerning (persistent suppression of bone turnover) biological properties of bisphosphonates. Although there may be merit to substances such as bisphosphonates that have a long half-life and once recycled maintain bone turnover, a downside could exist to this unique pharmacokinetic property as well. Denosumab is not retained in bone, and its duration of effect is short and reversible once discontinued.

This pharmacokinetic property of denosumab may also have its benefits as well as its downside. The increase in bone turnover and reduction in BMD seen within 1 year of denosumab's discontinuation could, theoretically, translate into transient impairment in bone strength. This important question may be answered by the planned extension studies of the phase 3 denosumab registration studies. Discontinuation of estrogen leads to an increase in bone turnover, although an increase in fracture risk has not been observed in the many estrogen withdrawal data, although the follow-up fracture data are not robust. In the NORA (National Osteoporosis Risk Assessment) study, a higher 1-year risk of hip fracture was seen in those women discontinuing estrogen, but in examining this specific aspect of the NORA population there was a substantial selection bias and low power to make definitive conclusions concerning bone strength associated with estrogen withdrawal-related increase in bone turnover [19]. Although in basic bone biology, high bone turnover and expansion of the remodeling space generally is associated with a reduction in bone strength, it is unknown if the increase in bone turnover after withdrawal of the effects of antiresorptive agents is also associated with an impairment in bone strength. Altering the remodeling space in treatment-naive patients may not have the same consequences on bone strength as in pharmacologically treated patients. For example, early increases in the remodeling space with teriparatide treatment are not associated with reduction in bone strength, probably due to
the compensation effects of increasing the cross-sectional moment of inertia mediated by teriparatide-induced new periosteal bone formation [21,22]. Because denosumab also increases cortical cross-sectional area, this favorable denosumab effect may also be protective. Denosumab’s availability for PPM management will offer a new choice for physicians to consider in their armamentarium of osteoporosis pharmacologic agents, one with novel mechanisms of action and that will also offer an easy and infrequent parenteral route of administration.

Conclusions
Denosumab (anti-RANKL antibody) is a fully human monoclonal antibody that reduces bone turnover and increases BMD at all skeletal sites, has a rapid offset of effect upon discontinuation, and a return of responsiveness upon rechallenge. Denosumab reduces fractures at all skeletal sites and has an excellent safety profile through 3 years of use. Denosumab’s case of administration (subcutaneous every 6 months) is very attractive and may offer better outcomes than current osteoporosis pharmacologic agents with poor adherence rates. This latter hypothesis needs investigation by head-to-head fracture comparisons.

Disclosure
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References and Recommended Reading
Lists of particular interest, published recently, have been highlighted as:
- Of importance
- Of major importance
