Commentary: Advances in Target-specific Therapy for Osteoporosis

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Bone is constantly being remodeled, with resorption preceding formation. In the individual who is not losing bone mass, bone remodeling is balanced, with the osteoblast forming the same amount of bone that has been resorbed by the osteoclast. Remodeling in the aging skeleton, aided and abetted by estrogen deficiency after the menopause, is not balanced, with bone resorption exceeding bone formation; as a result, bone loss ensues. The earliest therapeutic attempts to correct this imbalance were focused on inhibiting bone resorption, thus bringing the bone remodeling unit into better balance.

When alendronate, an amino-containing bisphosphonate, was approved by the FDA in 1995, (1–3) it was known that it reduced bone resorption, but the molecular mechanism of action (inhibition of a key enzyme in the mevalonate pathway, farnesyl pyrophosphate synthase) was not understood until later (4, 5). Subsequently, other bisphosphonates (risedronate, ibandronate and zoledronic acid) joined the family of approved bisphosphonates for the treatment of osteoporosis. Along with estrogen, raloxifene (an estrogen analog) and calcitonin, these agents together are called "antiresorptive" drugs. While it is true that their initial mechanistic effect is to reduced bone resorption, these drugs also reduce bone formation. Their therapeutic effect depends on the inhibition of resorption being greater than inhibition of formation. While the classification of these drugs as "antiresorptives" is not correct, since they are general antiremodeling agents, it is unlikely that other more accurate terms, such as "anticatabolic" or "antiremodeling" will replace the common classification that is universally used. These antiresorptive agents appear to be generally safe and well tolerated, and with specific reference to alendronate, risedronate and zoledronic acid, are associated with significant increases in bone mineral density (BMD) and reductions in the incidence of vertebral, hip and nonvertebral fractures. Despite their safety and efficacy, these drugs maintain skeletal microstructure but do not rebuild it.

In 2002, the therapeutic landscape for osteoporosis changed with the approval of teriparatide as a therapy for osteoporosis (6). Teriparatide is the aminoterminal sequence of human parathyroid hormone [rhPTH (1–34)]. Although chronically elevated levels of PTH cause bone loss by increasing bone resorption, intermittent use of teriparatide or the full-length molecule, PTH (1–84), is associated with a distinct osteoanabolic effect. The pharmacokinetics of this effect are described by an early increase in bone formation, rather exclusively, followed soon thereafter by an increase in bone resorption. Thus, an "anabolic window" is created, helping to explain the osteoanabolic properties of this drug. As with the bisphosphonates, the use of teriparatide for the treatment of osteoporosis was based on empiric observations, with the molecular mechanisms of action worked out only later. As noted for the "antiresorptive" agents, the terminology for teriparatide is a bit garbled because teriparatide's actions are not exclusively osteoanabolic. It effects are also associated in time with an increase in bone resorption. The osteoanabolic effect due to the anabolic window is relatively short-lived. The true osteoanabolic effect, namely when teriparatide is exclusively stimulating bone formation, is likely to be an increase in bone modeling, that is bone formation on quiescent bone surfaces. Similar in principle, however, to the antiresorptives (inhibition of bone resorption is chronically greater than inhibition of bone formation) the efficacy of teriparatide is prolonged beyond the modeling period, because bone formation exceeds bone resorption essentially for the entire 2-year ther-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received January 8, 2014. Accepted January 13, 2014.

Abbreviations:

apeutic period. For most of the time that teriparatide is exerting its beneficial skeletal effects, bone remodeling is stimulated. During this more prolonged remodeling period, the osteoanabolic window is actually kept open, albeit less so, because bone formation exceeds bone resorption. Teriparatide reduces the risk of vertebral and nonvertebral fractures. BMD increases somewhat more with teriparatide than with bisphosphonate therapy. Also different from the bisphosphonates and other antiresorptive drugs, skeletal microarchitecture is improved by teriparatide.

In 2010, denosumab, a novel "antiresorptive" agent, was approved on the basis of a large clinical trial showing "broad spectrum" antifracture efficacy (spine, hip and nonvertebral fracture risk reduction) (7) as well as relatively impressive increases in BMD over 3 years of treatment (7) with continuing gains in BMD through 8 years of continuous use (8). Denosumab represents a watershed moment in the history of pharmaceutics development for osteoporosis. While the bisphosphonates and teriparatide were developed rather empirically, without full knowledge of their molecular mechanisms, denosumab was specifically developed to inhibit a known molecule, RANK-ligand (RANKL). RANKL had been shown to be a very potent simulator of bone resorption by promoting progenitor osteoclast development and activation. The time from discovery of the RANK-RANKL-OPG pathway to the approval of denosumab was a remarkably short 15 years!

A second example of targeted drug development is cathepsin K-inhibition. Odanacatib was specifically developed to block cathepsin K, a key osteoclast enzyme involved in the resorption of bone matrix. Odanacatib impairs this aspect of osteoclast function but it does not interfere with its signaling capability to the osteoblasts. Thus, inhibition of bone formation occurs to a much smaller extent than is the case for the bisphosphonates and denosumab. As treatment with odanacatib is continued, bone formation markers return to baseline or rise somewhat higher, (9) making odanacatib a more pure "antiresorptive" drug. Results of a large phase 3 study with odanacatib are expected early in 2014.

Now another watershed moment in the history of targeted drug discovery for osteoporosis appears to be upon us. This development is based upon understanding of a key bone formation signaling pathway known as Wnt. The Wnt signaling pathway stimulates differentiation of precursors into mature bone-forming osteoblasts and is regulated in part by sclerostin, an osteocyte-secreted glycoprotein, that potently inhibits the pathway (10, 11). Sclerostin reduces osteoblast proliferation and function, thereby decreasing bone formation. The expression of the SOST gene, which encodes for sclerostin, occurs only in skeletal tissue, which makes inhibition of sclerostin an attractive target (11). The therapeutic principle is to inhibit sclerostin by an antisclerostin antibody and thus to permit unimpeded expression of the Wnt osteoanabolic pathway.

McClung et al have just published the results of a phase 2 multicenter study evaluating the effects of a romosozumab, a humanized antisclerostin antibody, in human subjects (12). The study enrolled 419 postmenopausal women with low BMD (T-score $<$-2.0 and $>$ –3.5) without a history of osteoporotic fractures in a 12-month protocol with lumbar spine BMD as the primary endpoint. All 5 doses of romosozumab (70, 140, or 210 mg SQ monthly, 140 or 210 mg SQ every 3 months) were associated with significant increases in BMD at the lumbar spine. The greatest gain was 11.3% percent above baseline for the 210 mg monthly dose, almost 3 times more than seen with alendronate (4.1%) and also significantly more than teriparatide (7.1%), two positive control arms of the study. Treatment with romosozumab also increased BMD in the total hip and femoral neck. There were no changes in BMD at the distal 1/3 radius with any romosozumab dose.

Changes in bone turnover markers, a secondary endpoint, gives rise to intriguing potential additional mechanisms. Bone formation markers increased very quickly, almost doubling within 1 month, but only transiently, beginning to return towards baseline by 2 months. By 12 months, the bone formation marker, P1NP, returned to baseline values. The bone resorption marker, β-CTX followed a pattern that is best described as a mirror image of the P1NP results. β-CTX falls as quickly as P1NP rises, reaching a nadir (about –50%) quickly, then rising to levels approaching baseline values. It appears though that bone formation exceeds bone resorption throughout the 12-month period. What is particularly fascinating is the potential mechanism by which romosozumab is having such a profound early effect on bone dynamics and BMD. With a clear inhibition of bone resorption while bone formation is showing a major increase, it is tempting to speculate that the drug is directly stimulating bone modeling; that is, bone formation on surfaces that were quiescent and not remodeling. It is reminiscent of the early effects of teriparatide but more profound. Different from teriparatide, in which there is a compensatory increase in bone resorption, there is no evidence for increases in bone resorption with romosozumab. This drug, therefore, may truly be best described as an osteoanabolic agent. The mechanism by which stimulating an anabolic signaling pathway can lead to a reduction in bone resorption remains to be investigated. Romosozumab was well toler-

ated in this phase 2 trial, except for mild, generally nonrecurring injection site reactions.

Advances in bone biology have catalyzed target-specific drug development for osteoporosis at a startling pace. Romosozumab is the latest example of this. We all look forward to the results of the phase 3 registration trials that are underway.

Acknowledgments

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Disclosures: *Nelson B. Watts,* Stock options/holdings, royalties, company owner, patent owner, official role: OsteoDynamics, cofounder, stockholder and director, Speaker bureau: Amgen, Merck, Novartis, Warner Chilcott, Consultant: AbbVie, Amarin, Amgen, Bristol-Meyers Squibb, Corcept, Endo, Imagepace, Janssen, Lilly, Merck, Novartis, Noven, Novo Nordisk, Pfizer/Wyeth, Quark, Radius, sanofiaventis, Research support: Merck, NPS, *John P. Bilezikian,* Advisory Boards: Amgen, Merck, Lilly, Consultant: NPS pharmaceuticals, Bristol Meyers Squibb, Johnson, Johnson, Research support: Amgen, NPS

This work was supported by .

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