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Summary

Summary - Novel Therapies for Osteoporosis

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Introduction

This session reviewed the status of ongoing new drug development. The discussion started with a review of the current status of pharmacologic interventions for treatment of established postmenopausal osteoporosis in order to provide a background for detailed review of drugs under development. For the purposes of this discussion, postmenopausal osteoporosis is defined as a DXA T-score <2.5, or a history of low-trauma fracture in a woman past menopause in the absence of identifiable cause. (It should be noted that the drugs used in women, for the most part, except for estrogens, are about equally effective in men.) The review examines the physiologic and pharmacologic (mechanism of action) details of new drugs under development rather than their clinical science. The session focused on new mechanisms of action and novel ideas for treatment targets. Currently available drug treatments act predominantly through one mechanism, suppression of remodeling, except for teriparatide. Teriparatide (parathyroid hormone, 1-34; PTH 1-34) is unique among them in that it *stimulates* remodeling and has a potent bone *anabolic* effect.

Anti-resorptive agents

The group includes estrogen, selective estrogen receptor modulators (SERMs), bisphosphonates and calcitonin. The remodeling suppressors have been referred to as "anti-resorptive" agents. However, while they do suppress bone resorption by osteoclasts, their effect is more complicated. A more accurate name might be "anti-remodeling" agents. Their primary action is to reduce the activation of new remodeling sites, leaving those sites that were in the formation phase of remodeling at the time of intervention to continue until completed. The most potent class of anti-remodeling agents is the amino-bisphosphonates. Their specificity for osteoclasts derives from the fact that they gain access to the intracellular space of osteoclasts through the bone resorption process. Other cells are protected because bisphosphonates do not readily penetrate cell membranes. A critical question regarding bisphosphonates' use is whether they over-suppress bone remodeling, thus weakening the skeleton because of inability to repair micro-damage. However, the suppression of remodeling is to a range seen in healthy, non-fracturing pre-menopausal women.

Hormone therapy (HRT)

Two classes of agents are included in this category, various estrogen preparations, and a SERM. Use of HRT is waning due to the problems uncovered in the Women's Health Initiative. However use of the SERM, raloxifene, has been steady. All of the currently approved treatments of osteoporosis, including raloxifene, have clinical anti-fracture efficacy supporting their use.

Novel treatments under development

Four novel treatments were presented, three representing variations on the anti-remodeling paradigm, and one anabolic agent that constitutes an alternative to teriparatide, namely intact human PTH (1-84).

Amgen is developing two agents that act through the RANKL/OPG pathway. This pathway is important in regulating the activation of remodeling on bone surfaces. RANK ligand (RANKL) binds to RANK (Receptor Activator NFκβ) to stimulate differentiation of osteoclast precursors into osteoclasts. OPG competes with RANKL to block its effect. Thus, development is progressing along two paths: 1) a fully human monoclonal antibody to RANKL that blocks its binding to RANK (AMG162), and 2) an fc fragment of OPG that competes with RANKL, preventing its binding. The RANKL antibody causes a dose-related sustained sup-

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pression of remodeling that lasts for months after a single injection. The OPG-fc also causes suppression of remodeling with weekly injections. In non-human primate studies, both cause significant increases in bone strength through increases in bone mass and improvement in architecture. Similar increases in bone mass and strength have been seen with AMG 162 in human studies. The RANKL antibody is under intense development that has progressed well into human studies. This represents a novel approach to anti-remodeling therapy that shows great promise.

Pfizer is developing an orally administered selective androgen receptor modulator (SARM) to stimulate the bone effects of androgens without stimulating the unwanted soft tissue effects such as prostate hypertrophy and HDL reduction. Several promising SARMS have been identified in cell culture screening and rodent studies that are truly selective in decreasing endocortical and trabecular remodeling, and stimulating bone apposition on the periosteal surface, the ideal location for maximum benefit to bone strength. At least one of these agents has demonstrated increases in muscle mass while decreasing fat mass. This line of development is early, and very exciting.

NPS Pharmaceuticals is developing parathyroid hormone 1-84 (PTH 1-84). This molecule is identical to human PTH, and the bone effects in primate models seem to be similar to teriparatide, the 1-34 amino acid peptide of human PTH. The primate experiments showed strong activation of remodeling, and strong anabolic effects. Further, the histomorphometry and micro-CT data show ideal anabolic effects; increased trabecular bone formation, increased trabecular bone volume, increased trabecular number, thickness and connectivity, and increased cortical bone. Interestingly, the histologic sections hint at a mechanism for the increase in trabecular connectivity. Thick trabeculae were observed in which "trabecular cutting cones" were seen dividing them into two. Biomechanical data demonstrate increases in bone strength, and the anabolic response seems to act through sensitizing the adaptive response to loading. Thus, the geometric arrangement of the new bone tissue is ideal from a biomechanical point of view. It is not yet clear how the effects of this agent differ from teriparatide.

Merck is developing an anti-remodeling agent along a path differing from the other anti-remodeling agents. The agent acts through inhibiting cathepsin K, the collagenase in osteoclasts that hydrolyzes type I collagen of bone matrix. Thus far, a number of agents have emerged from the chemical screening that show promising suppression of remodeling in rodent models. The agents show specificity for bone collagen since cathepsin K is unique to bone. Thus, other types of collagen are unaffected. This path of development is quite early, but shows exciting promise as an alternative method of suppressing remodeling.

Summary

The search for drugs that repair the skeletal fragility continues. The new paths seem promising and exciting. Stay tuned!