

Invited Speaker Abstract

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Osteoporosis therapeutics, current and future developments

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Over the past 13 years, an increasingly large number of drugs have become available for the prevention and treatment of osteoporosis. The therapeutics that dominate the landscape at this time are the so-called antiresorptive agents. They are called antiresorptive because they have, as a common denominator, an action to impair the activity of the bone-resorbing cell, the osteoclast. By inhibiting the osteoclast, the bone remodeling unit is brought into better balance and bone loss is curtailed. Along with estrogens, raloxifene (a selective estrogen receptor modulator), calcitonin, and bisphosphonates, a menu of options is available for physicians and patients. Some of these agents provide global protection against vertebral, non-vertebral and hip fracture while for others the evidence, based upon prospective clinical trial data, is limited to effects at vertebral sites. Teraparotide [PTH (1-34)] is the first member of a class called anabolics in which the primary therapeutic effect is not to influence bone resorption primarily, but rather to stimulate processes associated with bone formation. Teriparatide reduces vertebral and non-vertebral fractures with evidence for its therapeutic action including improved microarchitecture of bone. Adverse events occur with each of these agents but generally they are well tolerated and safe. When used in a program of nutritional repletion (calcium and vitamin D), exercise, life style optimization, and measures to prevent falls, we can be confident of a good end result, namely reduced fracture incidence.

At this time, new concepts are being explored that might lead to use of the agents we already have to even greater advantage. One area, for example, is combination therapy with an antiresorptive and teriparatide. Although initial studies did not support the idea that combination therapy was better than monotherapy, subsequent work has given reason to expect that under certain circumstances and with specific combinations, there might be advantages over monotherapy. Another aspect of combination therapy involves using agents in sequence such as using teriparatide after bisphosphonate therapy. This is an important issue because many patients who receive teriparatide have previously been treated with a bisphosphonate and also because a few reports have suggested under certain conditions there might be a delay in responsiveness to teriparatide if bisphosphonate therapy precedes its use. The OPTAMISE has explored this issue with regard to previous treatment with risedronate or alendronate. The results (Miller et al. JCEM, 2008, in press) will be presented and discussed.

On the horizon are newer classes of agents that have different mechanisms of action. For example, strontium ranelate is said to harbor both antiresorptive and anabolic actions. While this is only one of several mechanisms, strontium ranelate does reduce both vertebral and non-vertebral fractures. Even newer therapeutic concepts are being explored due to our greater understanding of the pathways by which bone cells are regulated. The RANK L-OPG system that is critically important for intercellular bone cell signaling can be perturbed by the use of a humanized antibody against RANK L. The antibody inhibits RANK L, a potent osteoclastic activator, leaving relatively unopposed the endogenous RANK L inhibitor, OPG to directly inhibit osteoclast action. The general mechanism utilized by the RANK L antibody therefore is ultimately an antiresorptive one but the means by which osteoclast action is impaired is uniquely different from any of the antiresorptives available at this time. The pivotal phase III clinical trial of Denosumab a humanized IgG anti-RANK L antibody, has just been completed and the results are expected soon.

Even newer therapeutic concepts, based upon anabolic pathways, are being developed at this time. The Wnt pathway, for example, is an essential means by which the osteoblast is regulated. Sclerostin, the SOST gene product, inhibits the Wnt pathway and is thought to serve as an endogenous control system. An antibody directed against sclerostin should release the Wnt pathway from that control and permit a greater anabolic

effect. Animal data are consistent with this idea. The presentation will offer additional ideas by which the Wnt signaling pathway could be modified and thus lead to a therapeutic effect.

One can return to the osteoclast and identify molecules that are essential to osteoclast action, such as cathepsin K, and consider means by which the osteoclast could be inhibited by interfering with cathepsin K activity. Cathepsin K inhibitor therapy is in clinical trials.

In summary, newer molecules are being developed to improve on what we have, to creatively use new combinations of approved drugs, and to take advantage of bone cell pathways of activation and inhibition.