Is it time to combine osteoporosis therapies?

Some therapies licensed to treat osteoporosis work by inhibiting bone turnover (anticatabolic agents) and some by stimulating bone formation (anabolic agents). In The Lancet, Joy Tsai and colleagues report an exciting new approach in which an anticatabolic drug, denosumab, is combined with an anabolic drug, teriparatide.

Teriparatide comprises the first 34 aminoacids of parathyroid hormone, and when given as a daily injection leads to an increase in bone-mineral density (BMD) of the spine and a reduction in spinal and non-spinal fracture risks. It was licensed in the UK in 2003, and is recommended by the National Institute for Health and Clinical Excellence for use in women who have severe osteoporosis and fragility fractures and in whom bisphosphonates have not been tolerated or have been ineffective. Loss of BMD from the hip, however, is frequently seen in the first 6 months of treatment, especially in patients who have previously been treated with bisphosphonates, although BMD does eventually increase over the recommended 2-year period of treatment. Avoidance of early bone loss in the hip would be preferable in order to prevent increased risk of hip fracture.

A seemingly obvious way to prevent bone loss from the hip would be to combine teriparatide with a bisphosphonate. This approach has been tried with oral alendronic acid given at a dose of 10 mg per day, but the overall increase in BMD at the spine and hip was reduced in women with established osteoporosis. Similar results were seen in men who were given alendronic acid and teriparatide and when a similar anabolic drug, intact parathyroid hormone, was given with alendronic acid in women with established osteoporosis. These findings were puzzling and led to the hypothesis that the inhibition of osteoclast survival by bisphosphonates also inhibits the secretion of an osteoclast-derived coupling factor that is necessary for the anabolic effect of teriparatide on osteoblasts.

Zoledronic acid is a bisphosphonate administered as a 5 mg infusion once per year. It suppresses bone resorption more rapidly and to a greater extent than alendronic acid (table). Greater attenuation of the effect of teriparatide than of alendronic acid would, therefore, be expected. The opposite, however, has been noted. In a 1-year study of zoledronic acid and teriparatide, alone or combined, zoledronic acid prevented early bone loss at the hip, but no additional benefit was seen at the spine compared with the effects of teriparatide alone. Thus, the hypothesis that the effect of teriparatide will be weakened might have to be altered to state that it applies only to anticatabolic therapies given orally on a daily basis. Denosumab is an anticatabolic drug that is given every 6 months by subcutaneous injection. It is an antibody to the receptor activator of nuclear factor κ B, and inhibits the key pathway by which osteoblasts and osteocytes regulate osteoclast activity. Bone resorption is more rapidly inhibited (within 24 h) than with zoledronic acid (table).

Tsai and colleagues describe a study in which 100 postmenopausal women with osteoporosis were randomly assigned to treatment with teriparatide and denosumab, alone or combined. As judged by the trial’s primary endpoint, posterior-anterior lumbar spine BMD, combination therapy was better than either drug alone, yielding an increase of 9.1% (SD 3.9) at 12 months as compared with an increase of 6.2% (4.6) with teriparatide and 5.5% (3.3) with denosumab. Femoral-neck and total-hip BMD also improved more with combination treatment than with teriparatide or denosumab alone. Therefore, the

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Denosumab is the most potent suppressor of bone resorption, but this suppression is not reversed when it is given in combination with teriparatide. ++=increased; --=decreased.

Table: Relative effects of anticatabolic treatments on bone resorption, formation, and net bone gain at the femoral neck.
Combination of denosumab and teriparatide seems to be more promising than the combination of zoledronic acid and teriparatide. Denosumab alone powerfully suppressed bone resorption and bone formation, but the denosumab and teriparatide combination suppressed bone formation less, which could explain the increased effect on BMD of the combination therapy. The improvement in total-hip BMD by almost 5% over 12 months is particularly impressive.

The finding of a greater change in BMD in the combined therapy group is consistent with results from studies of genetically modified mice; osteoclast activity did not seem necessary for the stimulation of bone formation by teriparatide in those studies.\(^1\) Tsai and colleagues provide proof of concept for the additive effect of combined teriparatide and denosumab over either treatment alone. Whether the combination remains effective needs to be investigated, however, because at 12 months mean concentrations of the bone formation marker PINP no longer differed between the denosumab-alone and combination-therapy groups. The safety of this combination therapy also needs to be explored, as does what happens when teriparatide is stopped (the licence only supports use for a maximum of 24 months). Finally, the reduction in fracture risk needs to be quantified so that cost-effectiveness can be assessed.

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