Drugs 2006; 66 (18): 2382-2385
0012-6667/06/0018-2382/$44.95/0

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Recombinant Full-Length Parathyroid Hormone (1-84)

A Viewpoint by David Hosking

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Bisphosphonate treatment is the gold standard for osteoporosis at the current time. These compounds work by inhibiting osteoclastic bone resorption. In the short term, they decrease the size of the remodelling space, delivering 'new' bone to areas of mechanical weakness. An inevitable consequence of this process is that bone turnover generally slows as the reduction in bone resorption will eventually be accompanied by a decrease in bone formation. Although the initial gain in bone mineral density (BMD) identified by dual-energy x-ray absorptiometry results from infilling of the remodelling space, subsequent slower gains in BMD reflect more complete mineralisation of the new bone.

The introduction of anabolic agents heralds a new era in the management of osteoporosis. Intermittent injection of low-dose parathyroid hormone (PTH) has an anabolic effect on bone by directly stimulating bone formation without the initial phase of resorption inhibition that occurs with bisphosphonates. Not only does PTH represent a new approach to the treatment of osteoporosis, it also challenges our assumptions about the measurements we use to assess response. Although it is recognised that an increase in BMD is only one component of the effect by which drugs reduce fracture risk, it nevertheless remains a common method of response measurement. However, the new bone laid down by PTH is less mineralised than established bone and this may lead to difficulty in interpreting changes in BMD where gains in BMD may not necessarily reflect the true extent of the anabolic effect. Partly because of this process, but also because gains achieved with PTH are lost when the drug is stopped, it will become common practice to follow anabolic therapy with established antiresorptive agents to maintain the gains in bone. By slowing turnover, antiresorptive drugs allow more time for bone to reach its potential for full mineralisation.

The introduction of a second commercially available form of PTH (PTH[1-84]) is to be welcomed because it enlarges the range of preparations that we have at our therapeutic disposal. However, it will be important to explore whether the differences between teriparatide and PTH(1-84) carry important clinical benefits in addition to those seen in animal experiments. Clinical studies are at an early stage and it is too soon to determine whether there are important biological differences between these two forms of PTH, or differences in their acceptability to patients. PTH is expensive and so it is important to couple the anabolic effect on bone with additional practical reasons for their prescription.

To some extent the initial studies with PTH(1-84) have been disappointing. The pivotal study did not show an effect on non-vertebral fractures (it was not designed to), although the studies confirm that a wide variety of patients with vertebral fractures respond very well. In some respects this is a problem of the current approach to clinical trials. Pivotal trials of PTH(1-84) and a recently introduced bisphosphonate, ibandronate, included patients who did not have a high risk of non-spine fractures and so it was almost impossible to demonstrate benefit. This is a particular puzzle when we see new drugs not achieving what seems to be a class effect, and it is a problem that is going to become more common if new agents have to be studied in placebo-controlled trials where it is unethical to include patients with a high fracture risk when established therapy is already available. ▲