

Teriparatide: anabolic action in osteoporosis

Mention possible endocrine causes of osteoporosis, and parathyroid hormone (PTH) and its catabolic actions on bone spring to mind. So the idea of treating this debilitating disease with a recombinant derivative of the human hormone's 34 N-terminal amino acids may seem surprising. But this derivative, teriparatide, has significant anabolic actions that lead to large rapid increases in bone mineral density (BMD) and reductions in fracture risk.

The anabolic actions of PTH were noted around 1930, but interest only grew 50 years later when the sequencing and synthesis of the N-terminus of human PTH (hPTH) allowed Reeve and colleagues to conduct the first formal clinical trial of 'intermittent' hPTH(1-34). Results were similar to those in animal studies, with a mean increase in trabecular bone volume of 70% above baseline. Moreover, the new bone was histologically normal. In 1997, the apparent dichotomy of action of PTH was demonstrated by Dobnig & Turner, who showed that intermittent exposure to hPTH(1-34) increased osteoblast number and bone formation in rats, whereas continuous exposure resulted in hypercalcaemia and abnormal bone histology.

During the 1990s, several large multicentre placebo-controlled randomised trials provided evidence for the prescription of anti-resorptive agents in osteoporosis. Bisphosphonates, HRT and specific oestrogen receptor modulators were all found to primarily inhibit osteoclast function, so reducing the rate of bone remodelling and allowing more complete secondary mineralisation of the existing bone matrix. But while this increased BMD, the bone's macro- and microarchitecture remained unchanged; anti-resorptives do not build new bone.

Previous attempts at anabolic therapy for osteoporosis either failed to show a significant anabolic effect (anabolic steroids) or were limited by increased fracture rates and unacceptable side effects (fluoride). In contrast, teriparatide's novel anabolic mechanism of action has provided a means of modulating and potentially partially reversing the pathology by primarily stimulating osteoblasts via the PTH/PTH-related protein receptor. Osteoblast number and function are increased, while osteoblast apoptosis is inhibited. The net result is increased bone formation, greater bone mass, and improved bone microarchitecture, including increased trabecular connectivity. This leads to a reduced rate of fractures.

A randomised controlled trial of teriparatide in 1637 postmenopausal women with osteoporosis has provided the most robust information about its use in clinical practice. Women who received 20µg daily by subcutaneous injection for around 18 months showed an increase in BMD of 9.7% at the lumbar spine and 2.6% in the total hip, compared with changes of 1.1 and -1.0% following placebo. At a higher dose (40µg daily) the changes were more marked, at 13.7 and 3.6% respectively. New vertebral fractures were seen in 14% on placebo, in contrast to 5% at the low dose and 4% at the high dose. Non-vertebral fragility fractures occurred in 5.5% of women in the placebo group but in 2.6% in each treatment group. The incidence of adverse events, particularly hypercalcaemia, was higher in the 40µg treatment group. Given the two doses' similarity in fracture reduction, 20µg was adopted as the recommended clinical dose. A subsequent subgroup analysis has indicated that bone density improvement and fracture risk reduction are largely independent of the initial bone density and fracture status. Similar changes in bone density are found following treatment of men with osteoporosis and in glucocorticoid-induced bone loss.

All these studies were conducted over a shorter period than usual for studies of osteoporosis treatment, as results of animal toxicology studies became available during the clinical development programme. Rats treated with high doses of teriparatide for most of their lifespan not only gained vast quantities of bone but also developed osteosarcoma. Given the high doses of treatment, the duration of therapy and the difference in bone turnover between rats and humans, these findings are probably not relevant to human treatment. However, this was not realised before the clinical trials had been terminated.

In the USA, teriparatide is licensed for use in both men and women with osteoporosis, whilst in the EU it has only been approved for women with established osteoporosis. The approved duration of treatment has been limited to 18 months, as this reflects the median duration of therapy before the pivotal clinical study was terminated. In addition, the contraindications (see list) reflect the need to avoid risk

factors for bone tumours, in addition to the more obvious exclusion of patients with pre-existing parathyroid activity or risk of developing hypercalcaemia.

The greatest restriction on teriparatide use is likely to be imposed by its cost. At £9.71 per day it costs ten times more than the most expensive conventional osteoporosis therapies. Guidance is being developed to identify patients in whom the extra expense is likely to be justified. In Scotland, the Scottish Medicines Consortium has approved its use for the treatment of severe osteoporosis under the supervision of an appropriate specialist. In England and Wales, the final results of a NICE technology appraisal are currently awaited. Meanwhile, the British Society for Rheumatology is producing guidance regarding the drug's use.

Teriparatide's novel anabolic mechanism provides a new approach for the management of osteoporosis, and its hormonal nature and administration by subcutaneous injection are familiar to endocrinologists. It may offer an opportunity for the speciality to once again become involved in the management of this common and disabling condition.

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Contraindications for teriparatide

- Hypersensitivity to teriparatide or any of its excipients
- Hypercalcaemia
- Severe renal impairment (plasma creatinine >160µmol/l)
- Metabolic bone diseases other than osteoporosis (including hyperparathyroidism and Paget's disease of bone)
- Unexplained elevation of alkaline phosphatase
- Prior radiotherapy to skeleton
- Prolonged immobility
- Metastatic bone disease
- Vitamin D insufficiency and/or secondary hyperparathyroidism
- Heterotopic or other secondary calcifying disorder