Anabolic treatment for osteoporosis: teriparatide

Richard Eastell
Jennifer S. Walsh

Academic Unit of Bone Metabolism, University of Sheffield, Sheffield, UK (R.E., T.V.)

Address for correspondence:
Prof. Richard Eastell, M.D., F.R.C.P., F.R.C. Path, FMedSci
Metabolic Bone Centre, Northern General Hospital
Herries Road, Sheffield, South Yorkshire, S5 7AU, UK
Phone: +44 (0)114 271 4705; Fax: +44 (0)114 261 8775
E-mail: r.eastell@sheffield.ac.uk

Summary
Teriparatide is a safe and effective anabolic treatment for osteoporosis. In postmenopausal women, it increases BMD and decreases vertebral fractures by about 70% and non-vertebral fractures by about 45% (although there is no evidence that it prevents hip fractures). The current evidence indicates that it should be administered for a single course of 24 months, and followed with an anti-resorptive agent to maintain the BMD gain.

There is no clear benefit to repeated or cyclical treatment. Combination treatment, particularly with denosumab achieves greater BMD increase than either agent alone, but there are no available fracture data for combination treatment.

There are some unknowns; most fundamentally why daily PTH administration is anabolic to bone when continuous high PTH is catabolic. Also, a better understanding of why the anabolic action declines with time and why there is a poor response to repeated treatment may help us to use teriparatide more effectively, and increase our understanding of bone biology and osteoporosis pathophysiology.

KEY WORDS: bone turnover markers; osteoporosis; bone formation; fracture; bone mineral density; teriparatide.

Introduction
Teriparatide refers to the molecule that makes up the first 34 amino acids of the intact parathyroid hormone (PTH, 84 amino acids). When PTH is given continuously, it stimulates bone resorption and loss of trabecular bone, as seen in endogenous primary hyperparathyroidism. When it is given intermittently, such as by daily injections, then it is anabolic and increases trabecular bone. It not only increases trabecular connectivity but also cortical thickness, based on microcomputed tomography studies of iliac crest bone biopsies (1). Teriparatide is the only current licensed anabolic treatment for osteoporosis in many countries. In most regions, it is restricted to second-line use as osteoporosis treatment due to greater cost than first-line agents such as alendronate. There is now extensive clinical experience with teriparatide, a good evidence base for its safety and efficacy, and some data on sequential or combination use with other osteoporosis drugs. However, there are still several unknowns around its mechanism of action, and why its anabolic effect decreases with time and repeated treatment. Intact parathyroid hormone has been licenced in Europe, but it is no longer available and so will not be discussed further. Abaloparatide is a modified version of the N-terminal region of parathyroid hormone-related protein that is currently in development for the treatment of osteoporosis but is outside the scope of this article.

Indications
The approved indications for treatment include the treatment of postmenopausal osteoporosis, male osteoporosis and glucocorticoid-induced osteoporosis. Teriparatide has been reported to improve bone mineral density in other clinical situations, such as osteogenesis imperfecta and anorexia nervosa, but it is not licenced for these indications, and so this is outside the scope of this article. We will focus on postmenopausal osteoporosis, but there is evidence for an increase in bone mineral density in men that is just as great as for women (2). In women and men with glucocorticoid-induced osteoporosis, there is evidence for anabolic effect as assessed by bone turnover markers and bone mineral density and there are fewer vertebral fractures than with treatment with alendronate (3).

In the UK, treatment is limited to patients with severe osteoporosis. In women, this means that they must be unable to take alendronate or else have an unsatisfactory response to alendronate (fracture or decrease in bone mineral density despite being compliant with medication for 12 months) (NICE TA161 https://www.nice.org.uk/guidance/ta161). Also, women over 65 years must have a T-score that is -4 and 3 or more fractures. Women under 65 years must have a T-score of -4 and 3 or more fractures. In women and men with glucocorticoid-induced osteoporosis, there is evidence for anabolic effect as assessed by bone turnover markers and bone mineral density and there are fewer vertebral fractures than with treatment with alendronate (3).
Duration of therapy

In Europe, the Summary of Product Characteristics (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000425/WC500027994.pdf) 15 January 2016) was changed to recommend ‘The maximum total duration of treatment with Forsteo should be 24 months. The 24-month course of Forsteo should not be repeated over the patient’s lifetime’. This recommendation about not repeating the dose, is in part based on safety (see below) and in part based on efficacy, as a second course given after a gap of 12 months only results in about one-third of the effect on BMD and bone turnover markers as the first course (4). Some of the anabolic effects of teriparatide are not manifest until months 18-24, so to obtain maximum benefit from treatment it is important to complete the whole course (5).

Safety

The original phase 3 study of teriparatide (6) was planned for three years but had to be stopped after a median duration of 19 months as there were bone neoplasms noted in F344 rat studies. This effect of teriparatide in rats is dose and duration-dependent (7). In the Fracture Prevention Trial, there were no cases of osteosarcoma and the risk of cancer overall was lower in the treated than in the placebo group (6). The initial post-marketing surveillance in the US between 2003 to 2009 did not reveal any cases of osteosarcoma with teriparatide use, despite identifying 1448 cases of osteosarcoma. A recent review (5) described three cases of osteosarcoma diagnosed during teriparatide therapy, although one of these occurred in a man with prostate cancer with previous irradiation. Osteosarcoma is no more common in primary hyperparathyroidism than in the background population (8, 9) and in a cohort of 582 patients with primary hyperparathyroidism, none developed osteosarcoma (8). Osteosarcoma is more common in patients with Paget’s disease of bone or those who have had radiation therapy and so teriparatide should not be used in these patients.

There are several side effects that can be related to hypercalcæmia resulting from teriparatide treatment. These include nausea, dizziness, headache, leg cramps and arthralgia. Hypercalcæmia was reported in 11% patients in the Fracture Prevention Trial when the blood sample was taken within 6 hours of dosing. It is best practice to monitor serum calcium on treatment and if serum calcium is above normal to lower the dose of calcium supplementation or stop it. If the patient remains hypercalcæmic, the dosing frequency of teriparatide can be reduced to alternate days. In most patients, symptoms due to hypercalcæmia are mild and transient.

There have been four reports of non-uraemic calciphylyaxis (10), but the extreme rarity means that physicians just need to be aware of this possible complication.

Efficacy

Fracture risk

The Fracture Prevention Trial included postmenopausal women with osteoporosis defined as at least two moderate atraumatic vertebral fractures, one moderate vertebral fracture and BMD T-score below -1.0, or two mild vertebral fractures and BMD T-score below -1.0. The relative risk of new radiographic vertebral fracture in women treated with teriparatide 20mcg vs placebo was 0.35 (95% CI 0.22 to 0.55), and the relative risk of nonvertebral fragility fracture was 0.47 (95% CI 0.25 to 0.88). The number of hip fractures (four in the placebo group and two in the 20mcg group) was too small to draw any conclusions about hip fracture.

In addition to the Fracture Prevention Trial, there have been two observational studies of teriparatide on fracture risk - Extended Forsteo Observational Study (ExFOS) (11) and Direct Assessment of Nonvertebral Fractures in Community Experience (DANCE) (12). These studies reported similar fracture risk reduction to the Fracture Prevention Trial; 75% reduction in clinical vertebral fractures and 49% reduction in all fractures in ExFOS, and 43 to 49% reduction in nonvertebral fractures in DANCE.

There have been no studies comparing shorter term (18 months) with longer term (24 months) teriparatide therapy on fracture risk. However, both ExFOS and DANCE reported that the later phases of the 24-month course were associated with lower rates of non-vertebral fracture than the earlier phases. In the Fracture Prevention Trial, there appeared to be a greater effect on non-vertebral fractures beyond one year than before one year (6). Lindsay analysed these data further to show that for each month of treatment the hazard ratio of non-vertebral fracture decreased by 7% (13).

Bone mineral density, geometry and bone strength

One of the largest prospective studies of teriparatide is the European Forsteo Study or EUROFORS. In this trial, a 24-month course of teriparatide therapy was associated with a progressive increase in both lumbar spine and total hip BMD in treatment-naïve patients (Figure 1). In patients on prior bisphosphonate, the increase at the total hip was not progressive as there was an early reduction in total hip BMD before the increase in the later months of treatment, particularly in those who were previously treated with alendronate or risedronate (14). Similar continued increases in BMD to 24 months have been reported in other studies (3, 15-17).

Quantitative computed tomography allows the study of bone strength by applying finite element models. This has been used for the spine, and it showed a progressive improvement over 24 months (18) and for the total hip where it also showed a progressive improvement over 24 months (19). Whitmarsh (2016) (20) used hip QCT to show that cortical thickness increases and density decreases in response to TPTD and endocortical trabecular density increases; the latter was greater if the treatment was for 24 rather than 18 months.

Bone turnover markers

Several bone turnover markers have been studied for monitoring response to teriparatide. The procollagen I N propeptide, PINP, has proven to have the greatest ‘signal to noise ratio’, and so it is the most suitable marker (21, 22). Bone formation markers increase within days of starting teriparatide and reach a peak between 6 and 12 months. They remain above baseline for the whole of the 24 month treatment period (15, 16). The markers even remain elevated in the setting of glucocorticoid-induced osteoporosis (3). The increase in PINP correlates with histological estimates of bone turnover by biopsy (15, 23, 24). Resorption markers increase later than formation markers, but also peak at 6-12...
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Figure 1 - EUROFORS Study: absolute BMD changes from baseline at the spine (A) and total hip (B). Numbers at the tops of the columns are the percent change from baseline. From Eastell (2009).

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months and remain above baseline throughout 24 months, consistent with ongoing remodelling (15).

**Bone histomorphometry**

There is an increase in bone formation rate after giving teriparatide. This is due to both an increase in the work of the cells (mineral apposition rate) and the number of the cells (mineralising surfaces as a proportion of total surfaces), and this was observed over a 24-month period for endocortical, intracortical and periosteal surfaces of the cortex (Ma 2014). There is an increase in both of these measures of bone formation by 6 months, and on most surfaces this increase persists to 24 months of treatment (25).

What happens after teriparatide therapy is stopped?

There are only two randomised controlled trials that allow study of the BMD effect of stopping teriparatide treatment compared to changing to another active drug and both used raloxifene. In one study (26), teriparatide was given for one year, and patients randomised to a further year of teriparatide, or a year of raloxifene or no active treatment and they gained a further 3.6%, no change, or lost 2.8% at the spine, respectively. In the other study (27), teriparatide was given for one year, and patients randomised to a year of raloxifene, or placebo and they lost 2.2% and 4.4% at the spine, respectively. The expected rate of bone loss in untreated postmenopausal women is 0.5 to 1.0% per year, so bone loss is accelerated when teriparatide is stopped.

The Fracture Prevention Trial was followed by an observational period during which patients could select to take bisphosphonates or take nothing over 18 months, and they gained about 3% or lost about 3% at the spine, respectively (28). This observational data in women is supported by observational data in men showing that bisphosphonates can prevent bone loss after stopping teriparatide (29, 30). There is also evidence that denosumab (31) and oestrogen (32) prevent bone loss after stopping teriparatide. Thus, accelerated bone loss after teriparatide treatment can be reduced to some extent by raloxifene. Follow-on treatment with bisphosphonates and denosumab prevent bone loss and may achieve further small increases in BMD. Therefore it is usually recommended in clinical practice to follow a course of teriparatide with an anti-resorptive drug. There is not yet evidence to determine how long this follow-on treatment should be continued.

What is the effect of a repeated course of teriparatide?

There is only one study that addresses this question. Finkelstein (2009) (4) administered an average dose of 30 mcg daily to men and women with osteoporosis for two years, gave a one year gap, then re-treated at the same dose for one year. They found that during the two-year period the anabolic effect assessed by bone turnover markers began to wane, as is usually observed and that there is very little biochemical response to a second period (Figure 2). Cosman treated patients with cyclical teriparatide – three months on and three months off – over 24 months and patients receiving this regime had significantly less BMD gain at 24 months compared with continuous daily treatment (33).

Mechanisms of apparent resistance

Why does teriparatide have less of an anabolic effect in the second year as compared to the first year of treatment and why is there little benefit from re-treatment? The apparent refractory nature of the bone to continued or repeated treatment could be due to the production of antibodies to teriparatide, but these have never been observed. There could be receptor downregulation as with repeated exposure to other hormones, or there may be a depletion of bone cell precursors. Why is there accelerated bone loss after stopping treatment? We don’t know the answer to any of these questions. Frost (2003) (34) proposed that when drugs are stopped then bone density should return to the baseline value as there is ‘disuse-mode remodelling’. He didn’t use this mechanism to explain apparent resistance although it is possible that this could be the mechanism. We don’t know how the changes in remodelling postulated by the mechanostat theory are mediated. One idea that has been proposed is
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that during teriparatide therapy there is an increase in Dick-
opr-1 (35), a negative regulator of bone formation, acting
through the Wnt pathway. Its levels increase, particularly
during the second year of teriparatide treatment and so
could mediate an apparent resistance.

Combination treatment

There is evidence to suggest that teriparatide could achieve
greater BMD increases in simultaneous combination treat-
ment with anti-resorptives. Teriparatide combined with zole-
dronic acid or denosumab increases BMD more than teriparatide alone (16, 36). Over 24 months, spine BMD increased 12.9% with denosumab and teriparatide, 9.5% with teriparatide alone and 8.3% with denosumab alone.

In the cyclical study, women treated with cyclical teriparatide and alendronate had similar BMD gain to women treated with continuous teriparatide, despite only receiving half the dose of teriparatide (33). However, in other studies co-treat-
ment with alendronate attenuated the BMD increase com-
pared with teriparatide alone, so there may be some com-
plexities in the interaction of alendronate and teriparatide
(37, 38).

Although combined treatment may achieve greater BMD gain, there are no fracture data to show that the combination has greater anti-fracture efficacy than single agent treat-
ment.

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