Osteoporosis in men: its pathophysiology and the role of teriparatide in its treatment

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Abstract: As the population ages, the burden of osteoporosis in men is expected to rise. Implementation of preventive measures such as falls prevention strategies, exercise and adequate calcium and vitamin D intake is recommended. However, when the diagnosis of osteoporosis is made, effective treatments need to be initiated to prevent fractures. As opposed to postmenopausal women, reduced bone formation is the predominant mechanism of age-related bone loss in men, making anabolic agents a logical treatment option for men with osteoporosis. Teriparatide is the only anabolic agent currently approved for treatment of osteoporosis in men. This paper summarizes the mechanism of action of teriparatide, as well as its tolerability and safety. Furthermore, the evidence supporting the efficacy of teriparatide treatment in men with osteoporosis is reviewed and its current role in the management of osteoporosis in men is discussed.

Keywords: osteoporosis, pathophysiology, treatment, parathyroid hormone, men

Osteoporosis in men
Scope of the problem

Although the majority of research on osteoporosis in the past has focused on women, osteoporosis is also becoming an increasingly important problem in men. One in 8 men aged over 50 will have an osteoporosis-related fracture (Cooper and Melton 1992) and this figure is predicted to rise with an aging male population (Burge et al 2007). Although fragility fractures in men occur an average of 10 years later compared with those in women (Bilezikian 2000), most clinical fractures result in greater morbidity and mortality (Johnell et al 2001). Hip fractures are the most important for health outcomes, quality of life, and costs (Chang et al 2004) with mortality reaching 37.5% in the year after the fracture (Jiang et al 2005). Vertebral fractures also carry their share of morbidity and mortality in men. Even though most vertebral fractures are painless, they are associated with height loss, reduced quality of life, respiratory dysfunction, social withdrawal (Burger et al 1997; Scane et al 1999) and decreased survival (Lau et al 2008). Finally, a history of low-trauma fracture, including asymptomatic vertebral fracture, increases the risk for hip and other clinical fractures (Melton et al 1999; Klotzbuecher et al 2000). However, despite these alarming statistics and the availability of effective treatment options, osteoporosis continues to be under-recognized in men, with the majority of those with fractures going untreated (Meryn 2005).

Factors contributing to osteoporosis in men

Osteoporosis in men can be classified as primary or secondary, with primary osteoporosis often divided into idiopathic and age-related based on the age of diagnosis. Primary osteoporosis comprises approximately half the cases in men and is a heterogeneous multi-factorial condition referring to the development of osteoporosis when no secondary cause is identified (Khosla et al 2008).
Age-related bone loss usually occurs in men over the age of 70 years due to a combination of nutritional and hormonal deficiencies (Khosla et al. 2008). The decrease in intestinal calcium absorption and high prevalence of vitamin D insufficiency and deficiency seen in elderly men both contribute to elevated serum parathyroid hormone (PTH) levels and bone loss (Lips 2001). Other potential mechanisms by which sufficient vitamin D levels might preserve bone health are induction of osteoblastogenesis and osteoblastic activity, activation of osteogenic genes, prevention of osteoblast apoptosis and inhibition of bone marrow adipogenesis (Duque et al. 2004a, b, 2005). Many other hormonal factors have also been incriminated in the pathophysiology of age-related bone loss in men. Both free or bioavailable testosterone and estradiol levels decline with age due to increased serum sex-hormone binding globulin (SHBG) levels and failure of the hypothalamic-pituitary-testicular axis to compensate (Khosla et al. 1998; Orwoll et al. 2006). Although cumulating evidence supports a dominant role of estrogen in maintaining bone mass in men, testosterone also contributes (Falahati-Nini et al. 2000; Leder et al. 2003; Amin et al. 2006). Age-related decreases in insulin-like growth factor 1 (IGF-1) and increases in insulin-like growth factor binding protein 2 (IGFBP-2) levels may also impair bone formation directly or via an increase in serum SHBG levels (Amin et al. 2004, 2007).

On the other hand, 85% of cases of secondary osteoporosis in men are explained by glucocorticoid use, hypogonadism, and excessive alcohol intake (Ebeling 1998, 2008). These factors are present in the majority of younger men with osteoporosis (Orwoll and Klein 2001) and may be superimposed on primary osteoporosis (Khosla et al. 2008).

**Pattern of bone loss in men – importance of reduced bone formation on trabecular and cortical bone loss**

Both trabecular and cortical bone loss contribute to an age-related reduction in bone mass. Trabecular bone, predominantly found in the vertebrae, begins to decline before midlife in both sexes, but to a lesser extent in men, with 42% of trabecular bone being lost before age 50 (Riggs et al. 2008).

In contrast, cortical bone mass remains relatively stable until midlife, then decreases linearly in both men and women, with the decline being greater in females (Riggs et al. 2008). Cortical bone loss occurs later in life from around the age of 65 years in men, as the total surface available for trabecular remodeling decreases, causing bone remodeling to move from the trabecular to cortical compartment (Seeman 2002). The balance between endosteal bone resorption and simultaneous periosteal apposition determines the net decrease in cortical bone area. Although the amount of endosteal bone lost during aging is similar in men and women, periosteal bone gained is greater in men (Garn et al. 1972; Seeman 2002; Ahlborg et al. 2003). Structural failure emerges during ageing because periosteal bone formation incompletely offsets fragility produced by bone loss and architectural destruction inside bone.

The pattern of age-related changes in bone structure is an important factor in the pathophysiology of bone loss. In men, trabecular bone loss occurs by reduced bone formation, resulting in trabecular thinning, with maintenance of trabecular number and connectivity. Conversely, bone resorption is the predominant mechanism of bone loss in postmenopausal women, resulting in a greater reduction in trabecular number and subsequent loss of connectivity and trabecular perforation (Aaron et al. 1987) (Figure 1). Although both trabecular thinning and reduced trabecular number are associated with lower bone density, the latter has the greatest impact on bone strength (Silva and Gibson 1997), explaining in part the lower lifetime risk of fractures in men.

**Current management of osteoporosis in men**

**Preventive measures**

**Exercise and falls prevention**

In healthy older men, high-intensity progressive resistance training, weight-bearing impact exercise, or the combination of the two, increased bone mineral density (BMD) compared with controls (Kukuljan et al. 2006). Although clinical trials have not yet shown that these BMD changes translate into reduced fracture risk, observational data suggests that older men who maintain an active lifestyle have a lower fracture risk (Michaelsson et al. 2007). Meta-analyses of trials in older adults show that balance and strengthening exercises reduce the risk of falls (Carter et al. 2001; Lord et al. 2003), and given that a propensity to fall puts people with osteoporosis at greater risk for fracture, falls prevention strategies should be implemented (Tinetti 2003).

**Calcium and vitamin D**

Although data on the benefit of calcium and vitamin D on fracture prevention are inconsistent, a recent systematic review of 17 randomized trials involving over 50,000 participants showed that calcium alone or in combination with vitamin D reduces osteoporotic fractures by 12% among both men and women aged over 50 (Tang et al. 2007). When analysis was performed on the 8 trials (n = 4,508) that reported a compliance rate of at least 80%, the risk reduction was doubled (24%). The treatment effect was also greater...
when at least 1,200 mg of calcium and 800 IU of vitamin D were taken. Vitamin D doses of at least 800 IU daily are therefore recommended, with the goal of maintaining a serum 25-hydroxyvitamin D level $\geq 30$ ng/mL (75 nmol/L) (Vieth et al 2001).

**Pharmacotherapy**

Pharmacological agents have not been as well studied in men with osteoporosis as in women, and only a few treatments have been approved for use in men. These include bisphosphonates and teriparatide.

**Bisphosphonates**

Bisphosphonate therapy has been shown to be effective in increasing BMD in men with primary osteoporosis, as well as in men with secondary osteoporosis, including hypogonadism and glucocorticoid-induced osteoporosis (Orwoll et al 2000; Ringe et al 2006). Although most trials of oral bisphosphonates in men have been either underpowered or not primarily designed to assess their effect on fracture incidence, some trials showed a significant 60%–88% reduction in the occurrence of new radiologic vertebral fractures (Orwoll et al 2000; Ringe et al 2006). Although the increase in BMD with bisphosphonate therapy is similar in men and women (Ho et al 2000) and could therefore theoretically translate into a reduction of fracture risk similar to the one observed in women, more data are required to ascertain the benefits of oral bisphosphonates on non-vertebral and hip fractures in men. Zoledronic acid is a potent intravenously administered bisphosphonate whose effects on fracture risk been assessed in a recent randomized placebo-controlled trial involving elderly men and women who had recently suffered a hip fracture (Lyles et al 2007). Yearly administration of 5 mg of zoledronic acid for a median of 1.9 years within 3 months of the fracture reduced the occurrence of overall new clinical fractures and mortality, but not hip fractures. Bisphosphonates are generally well tolerated. However, both intravenous and oral bisphosphonates have been linked in rare cases to osteonecrosis of the jaw, although current limited data suggest no clear increase in the risk of this complication in patients with osteoporosis (Bilezikian 2006). Rare case reports of atypical femoral diaphyseal fractures in patients on bisphosphonate therapy have also recently emerged in the literature and raise concerns about the long-term safety of this treatment in some individuals (Goh et al 2007; Lenart et al 2008; Visekruna et al 2008). However, more data are required on these atypical fractures.

**Teriparatide as a new option for the treatment of osteoporosis in men**

**Teriparatide: why is it different?**

Anticatabolic therapies such as bisphosphonates act by inhibiting osteoclast activity causing a decrease in bone resorption and depth of resorption cavities. Because bone remodeling is a coupled process, this decrease in osteoclast activity is accompanied by a decrease in osteoblast activity (Balena et al 1993; Draper et al 1996). This low turnover state leads to an improvement in BMD by increasing the time for matrix mineralization (Meunier and Boivin 1997). Anticatabolic therapies halt bone loss but do not add new...
bone, nor do they restore disrupted microarchitecture. In severe cases of osteoporosis, putting a stop to further bone loss may not be enough to prevent further fractures. In these cases, treatments that stimulate bone formation and reverse skeletal deterioration may provide a valuable treatment option (National Cancer Institute 2001). In men, where decreased bone formation is an important etiological factor, an anabolic treatment seems a logical approach. Teriparatide is the only anabolic agent currently approved for treatment of osteoporosis in men.

**Molecular structure of parathormone and teriparatide**

The native hormone secreted by the parathyroid gland chief cell is human parathyroid hormone [hPTH (1–84)], a single-chain polypeptide with 84 amino acids (Quattrocchi and Kourlas 2004). The knowledge of the molecular structure of PTH allowed the production of hPTH (1–84) for treatment in humans. Moreover, the discovery that the N-terminal 34 amino acid portion of the native PTH molecule could fully activate the PTH/PTHrP receptor (Reeve et al 1980) led to the generation of pharmacological products comprising only this portion, such as hPTH (1–34) and recombinant human PTH [rhPTH (1–34)]. Teriparatide is the generic name for all PTH (1–34) molecules.

**Anabolic effects of teriparatide on bone**

Continuous high circulating PTH levels versus intermittent peaks of PTH have opposite effects on bone metabolism. The former has catabolic effects on bone as shown in people with primary hyperparathyroidism whereas administration of low-dose (20 μg/d), intermittent PTH, has an anabolic effect (Tam et al 1982). Although there have been advances in understanding the molecular and cellular events associated with activation of the PTH receptor in bone, the mechanism of action of teriparatide remains incompletely elucidated. Based on bone marker studies, teriparatide increases both bone formation and resorption. However, in the first 3 months of treatment, there is a period known as “the anabolic window” where PTH stimulates bone formation to a greater extent than bone resorption, suggesting that teriparatide could initially induce bone apposition without prior bone resorption through modeling-based formation (Dempster 2001; Bilezikian 2008). After 3–6 months of teriparatide treatment, the bone remodeling rate is globally increased, with bone formation favored over bone resorption resulting in a net gain of bone deposited in each basic multicellular unit (BMU). Teriparatide’s effect on bone formation is mediated by an increase in the number of osteoblasts via activation of osteoprogenitor differentiation and prevention of osteoblast apoptosis (Nishida et al 1994; Jilka et al 1999). Its anabolic effect on bone could also be indirect, through induction of IGF-1 synthesis in osteoblasts and downregulation of growth factor antagonists, such as sclerostin (Canalis et al 1989; Miyakoshi et al 2001; Bellido 2006).

**Safety and tolerability**

**Frequent adverse effects**

Adverse events reported during large phase III trials with teriparatide have generally been mild (Orwoll et al 2003). Most frequent adverse events associated with teriparatide 20 μg sc daily were dizziness and leg cramps, and these occurred in fewer than 10% of treated patients. Injection site hypersensitivity occurred in a small number of patients. Allergic reactions, including dyspnea, urticaria, and chest pain, occurred in fewer than 1 in 1000 teriparatide recipients (Gold et al 2006).

**Hypercalcemia and hypercalciuria**

Six percent of men experienced mild transient hypercalcemia in phase III trials. It appeared generally 4–6 hours after teriparatide administration and resolved within 24 hours (Orwoll et al 2003). If hypercalcemia occurs, it is generally recommended to reduce calcium intake to 1,000 mg daily or less or to decrease the dose or frequency of teriparatide. Monitoring of serum calcium is not considered to be a routine requirement during treatment with teriparatide. However, measuring serum calcium at baseline and after a month of therapy could be a good practice (Stroup et al 2003; Hodsman et al 2006). Likewise, a recent study evaluating the effect of teriparatide on urinary calcium at 1, 6, and 12 months in two large placebo-controlled trials (Neer et al 2001; Orwoll et al 2003) showed that increases in urinary calcium excretion were small and that less than 1% of the participants required a change in calcium or teriparatide dose due to hypercalciuria (Miller et al 2007). Since subjects with impaired renal function or with a history of kidney stones were excluded in these trials, it might be considered to monitor urinary calcium in patients with hypercalciuria at baseline or with a history of urolithiasis; however, no firm guidelines have been established on the follow-up of this rare adverse effect (Hodsman et al 2006; Miller et al 2007).

**Osteosarcoma**

So far, only one case of osteosarcoma associated with teriparatide has been reported in humans (Harper et al 2006).
However, causality between teriparatide and osteosarcoma in this patient has not been established, as this was a single case among more than 300,000 patients worldwide treated with teriparatide, which is similar to the background incidence of osteosarcoma in the general population of men and women over 60 years of age. The fact that this case of osteosarcoma was detected early in the course of teriparatide also led to speculation it was pre-existing. Nevertheless, close monitoring for incident cases of osteosarcoma in patients treated with teriparatide should be continued. In addition, teriparatide treatment should be avoided in patients at increased baseline risk for osteosarcoma, such as those with Paget’s disease, unexplained elevations in alkaline phosphatase, or prior radiation therapy involving the skeleton. Its use should also be limited to two years because safety and efficacy for longer periods have not been evaluated (Stroup et al 2008).

### Efficacy studies of teriparatide in men

#### Effects of teriparatide on biochemical bone markers

Markers of bone formation include bone specific alkaline phosphatase (ALP), osteocalcin (OC), and C-terminal and N-terminal propeptides of type one procollagen (PICP and PINP), whereas urinary free pyridinoline (PYD), free deoxypyridinoline (fDPD), and N-telopeptide (NTX), as well as serum C-telopeptide, are markers of bone resorption. The measurement of bone markers in clinical trials have helped better understand the mechanism of action of teriparatide and to determine the role of these markers in the prediction and assessment of the response to treatment in both men and women with osteoporosis. Three studies conducted in men with osteoporosis have evaluated the effects of teriparatide on bone markers (Kurland et al 2000; Orwoll et al 2003; Finkelstein et al 2006). Markers of bone formation (bone ALP and PICP) and resorption (NTX and fDPD) were measured at baseline, 1, 3, 6, and 12 months following treatment with teriparatide 20 or 40 μg daily in 437 men with primary osteoporosis or osteoporosis due to primary hypogonadism (Orwoll et al 2003). Teriparatide caused significant dose-dependent increases in both markers of bone formation and resorption. One month after teriparatide 20 μg daily, PICP levels reached their maximum (~30% increase from baseline) while the ratios of urine NTX and fDPD corrected for creatinine were only marginally increased. Similar greater increments of markers of bone formation over bone resorption were reported in the first 1–3 months of treatment when PICP, OC, and P1NP were measured (Kurland et al 2000; Finkelstein et al 2006). Changes in bone resorption markers after teriparatide treatment were similar between studies with peak levels at 6–12 months. Of interest is the distinct pattern of response between bone formation markers in the study by Orwoll et al. As opposed to PICP, the increment of bone ALP was gradual, reaching a peak at 6 months (Figure 2). These findings suggest that different bone formation markers provide information on different aspects of osteoblast function and might not be interchangeable (Orwoll et al 2003).

Two studies have provided insight on the possible role of bone markers to predict the response to teriparatide (Kurland et al 2000; Dobnig et al 2005). The first study, conducted in men with idiopathic osteoporosis, found that the change in OC at 3 months together with baseline PYD contributed 70% to the variance in lumbar spine BMD after 18 months of teriparatide treatment (Kurland et al 2000). In postmenopausal women, early increases in bone formation markers, and especially bone ALP, correlated with improvements in bone structure after 22 months of rPTH (1–34) (Dobnig et al 2005). However, no studies in men have assessed the role of bone markers to predict bone structure.

In summary, greater and earlier increases in bone formation markers compared with bone resorption markers after teriparatide therapy suggest that bone gain initially results from modeling-based bone formation without prior bone resorption. Later, stimulation of bone remodeling and in particular, bone formation, by teriparatide, provides additional bone gain. This is in contrast with reductions in bone markers typical of anti-resorptive therapy. As for bisphosphonates, it appears that bone markers could be useful as predictors of response to teriparatide treatment, particularly PINP and PICP.

#### Effects of teriparatide on BMD and fracture risk (Table 1)

Two main studies have evaluated the effect of teriparatide on BMD in men (Kurland et al 2000; Orwoll et al 2003). In the first study, 23 men aged between 30 and 69 years with idiopathic osteoporosis and with or without a previous fracture (prevalence of fracture of 70% and 90% in the placebo and treatment groups, respectively) were randomized to either placebo or 400 IU (25 μg) of hPTH (1–34) for 18 months (Kurland et al 2000). BMD was measured at baseline and every 6 months at the lumbar spine, hip and radius. A linear increase in lumbar spine BMD was observed in the treatment group and was already significant at 6 months (4.8 ± 2.0% at 6 months and 13.5 ± 3.0% at 18 months), whereas no significant change was remarkable in the placebo group.
In contrast, the increase in BMD at the femoral neck in men treated with teriparatide was slower, only reaching significance at 18 months (2.9 ± 1.5%; p < 0.05). Finally, the treatment group experienced a small and non-significant 1.2 ± 0.6% decline in BMD at the 1/3 site of the radius compared with baseline. These results were reproduced in a study involving 437 men aged 30–85 years with primary osteoporosis or primary hypogonadism treated for a median of 11 months with either rPTH (1–34) 20 or 40 μg daily or placebo. Although the increase in lumbar spine BMD was less in this study, it was already significant at 3 months (Orwoll et al 2003) (Figure 3). The response to teriparatide treatment was independent of gonadal status, alcohol intake or age.

None of these studies was specifically designed to address the effect of teriparatide on fracture risk in men. To our knowledge, the only study that evaluated this endpoint is a follow-up of the previously mentioned study conducted by Orwoll et al (Kaufman et al 2005). Eighty-one percent of the initial cohort of 437 hypogonadal or eugonadal men with osteoporosis were enrolled in the 30-month follow-up study. Of these, 41% had known vertebral fractures at baseline. Baseline radiographs of the thoraco-lumbar spine before initiation of teriparatide were compared with those 18 months after discontinuation of therapy in 279 subjects. There was a trend for the risk of new vertebral fractures to be reduced by 51% (p = 0.07) in men who received teriparatide, corresponding to an absolute risk reduction (RR) of 6%. Of particular interest is the 83% reduction in the incidence of moderate or severe vertebral fractures in the combined teriparatide groups (absolute RR 5.7%; p = 0.01). Of the 114 men with vertebral fractures at baseline, the
absolute RR for a new vertebral fracture was 13% in those assigned to the treatment group and no participant in this group experienced a moderate or severe fracture ($p = 0.002$ vs placebo). This study was not powered to evaluate the effect of treatment on the incidence of non-vertebral or hip fractures.

### Combination therapy with teriparatide and alendronate

Since teriparatide increases both bone formation and resorption, the combination with an anti-resorptive agent could theoretically have synergistic effects on BMD. However, studies in both men and women have clearly shown that bisphosphonates impair the ability of teriparatide or PTH (1–84) to increase BMD (Neer et al 2002; Black et al 2003; Finkelstein et al 2003). The relative efficacies of alendronate, teriparatide or a combination of the two were assessed in a study of 83 men with low BMD (Finkelstein et al 2003). Participants were randomly assigned to receive alendronate 10 mg/day, PTH 40 $\mu$g/day, or both treatments for 30 months. The PTH-alone group had BMD increases of 18.1% at the posteroanterior spine and 9.7% at the femoral neck. These increases were significantly greater than those observed in both the alendronate arm (7.9% and 3.2%, respectively) and in the combination therapy arm (14.8% and 6.2%, respectively). These findings raise the possibility that bone resorption is required for teriparatide to increase bone formation. Measurement of bone markers in this study revealed that alendronate impaired the ability of teriparatide to increase bone formation and bone resorption markers, therefore supporting this hypothesis (Finkelstein et al 2006). Indeed, prior bone resorption may release preformed growth factors necessary to trigger the anabolic effect of teriparatide (Oreffo et al 1989). However, a direct effect of

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### Table 1: Studies evaluating the efficacy of teriparatide in men with osteoporosis

| First author year | n | Baseline characteristics | Treatment duration | Treatment | Percent change in BMD at the lumbar spine | Percent change in BMD at the femoral neck | Percent change in BMD at the 1/3 site of the radius | Vertebral fracture reduction |
|-------------------|---|--------------------------|-------------------|----------|-------------------------------------------|------------------------------------------|------------------------------------------------|-----------------------------|
| Kurland 2000      | 23 | • Idiopathic osteoporosis <br>• Low bone turnover <br>• Fracture history or back pain <br>• LS T-score –3.4 <br>• FN T-score –2.0 | 18 mo | Teriparatide 400 IU/d (25 $\mu$g) Placebo | 13.5 ± 3.0<sup>c</sup> | 2.9 ± 1.5<sup>c</sup> | –1.2 ± 0.6<sup>c</sup> | • Insufficient power |
|                   |   |                          |                   |          |                                           |                                           |                                           |                             |
| Orwoll 2003       | 437 | • Hypogonadal (49%) or eugonadal <br>• LS T-score –2.2 <br>• FN T-score –2.7 | 11 mo (median) | Teriparatide 20 $\mu$g/d | 5.9 (5.2, 6.6)<sup>c,d</sup> | 1.5 (0.9, 2.2)<sup>c,d</sup> | –0.5 (–0.8, –0.1) | • 51% RRR fractures<sup>a</sup> |
|                   |   |                          |                   | Teriparatide 40 $\mu$g/d | 9.0 (7.9, 10.1)<sup>c,d</sup> | 2.9 (1.9, 4.0)<sup>c,d</sup> | –0.6 (–0.9, –0.2) | • 83% RRR moderate/severe fractures<sup>a</sup> |
|                   |   |                          |                   | Placebo | NS | NS | NS |                             |
| Finkelstein 2003  | 83 | • Primary osteoporosis <br>• LS or FN T-score ≤ –2.0 | 30 mo (median) | Teriparatide 40 $\mu$g/d | 18.1 (14.9, 21.3)<sup>e,f</sup> | 9.7 (6.1, 13.4)<sup>e,f</sup> | –0.8 (–2.3, 0.6)<sup>e,f</sup> | •                             |
|                   |   |                          |                   | Alendronate 10 mg/d | 7.9 (6.3, 9.4)<sup>e</sup> | 3.2 (1.5, 4.8)<sup>e</sup> | 1.0 (0.2, 1.8)<sup>e</sup> |                             |
|                   |   |                          |                   | Both<sup>b</sup> | 14.8 (12.4, 17.3)<sup>e</sup> | 6.2 (4.0, 8.4)<sup>e</sup> | 1.0 (–0.1, 2.1)<sup>e</sup> |                             |

<sup>a</sup>Mean percentage change in BMD ± SEM or mean percentage change in BMD (95% CI) at the study endpoint.

<sup>b</sup>Teriparatide was begun at month 6.

<sup>c</sup>$p < 0.05$, teriparatide 20 $\mu$g/d vs 40 $\mu$g/d vs placebo.

<sup>d</sup>$p < 0.05$, teriparatide 20 $\mu$g/d vs 40 $\mu$g/d.

<sup>e</sup>$p < 0.05$, teriparatide 40 $\mu$g/d vs alendronate.

<sup>f</sup>$p < 0.05$, teriparatide 40 $\mu$g/d vs combination alendronate 10 mg/d and teriparatide 40 $\mu$g/d.

<sup>g</sup>$p < 0.05$, alendronate 10 mg/d vs combination alendronate 10 mg/d and teriparatide 40 $\mu$g/d.

<sup>h</sup>Comparison of radiographs at baseline and 18 months after discontinuation of teriparatide or placebo in 279 of the 355 subjects who enrolled in the follow-up study (Kaufman et al 2005). At that time, 36% and 25% of the men who were previously in the placebo and combined teriparatide arms, respectively, were receiving an anti-osteoporosis drug. Bisphosphonates accounted for 75% of osteoporosis therapy and testosterone was the second most common.

Abbreviations: LS, lumbar spine; FN, femoral neck; BMD, bone mineral density; Mo, months; NS, not significant; RRR, relative risk reduction.
alendronate on osteoblasts cannot be excluded and it is still possible that teriparatide stimulates directly bone formation independently of its effect on bone resorption through mechanisms previously explained. In conclusion, these data indicate teriparatide should be initiated as monotherapy, because combination with anti-resorptive agents attenuates its anabolic effect.

**Effect of previous bisphosphonate therapy on efficacy of teriparatide**

Given that teriparatide is costly and generally approved as second-line therapy in most countries, the great majority of men with osteoporosis encountered in clinical practice will have already received a course of bisphosphonates prior to initiation of teriparatide. The ensuing important question is whether previous treatment with bisphosphonates reduces the efficacy of teriparatide. Finkelstein et al (2006) compared the increase in bone formation and bone resorption markers following teriparatide started at baseline for 30 months or preceded by 6 months of alendronate 10 mg daily in 63 men with low bone mass. Alendronate clearly reduced the ability of teriparatide to increase both bone formation and resorption markers. In the only study including men (29 men and 35 women) with osteoporosis, Handler retrospectively compared the effect of 18–24 months of teriparatide on BMD in patients previously treated with iv bisphosphonates (group 1, n = 36) or oral bisphosphonates (group 2, n = 16) vs treatment naïve patients (group 3, n = 12) (Handler 2008). Annualized average BMD gain, assessed by spine computerized vertebral tomography (QCT), was 7%, 4%, and 16% in groups 1, 2, and 3, respectively. Patients who received iv or oral bisphosphonates were also more likely than treatment naïve patients to be non-responders (14% and 25% vs 0%, respectively) defined as further bone loss or <1% annualized gain under treatment. Of interest, the time lag between the last dose of bisphosphonate and initiation of teriparatide positively influenced the response to teriparatide. Although current evidence in men is scarce, it is consistent with a blunting of the effect of teriparatide on bone markers and BMD when administered after a course of bisphosphonates.

**Initiation of therapy after discontinuation of teriparatide**

Because of the osteosarcoma concerns, teriparatide therapy is currently approved for 18 to 24 months, depending on the country. After this period, switching to a bisphosphonate is recommended to maintain and perhaps increase the gains obtained during teriparatide treatment. Indeed, rapid loss of BMD occurred after discontinuation of teriparatide on
men with idiopathic osteoporosis (Kurland et al 2004). Furthermore, additional gains in lumbar spine BMD were demonstrated if a bisphosphonate was administrated immediately after cessation of hPTH (1–34), with a 4-fold cumulative increase in lumbar spine BMD at two years in those who took a bisphosphonate compared to those who delayed bisphosphonate therapy or who received no treatment (23.6%, 11.1%, and 5.5%, respectively). Noteworthy, the use of teriparatide for a mean of 22 months did not appear to blunt the ability of bone to subsequently respond to a bisphosphonate. These findings are interesting and suggest that when bisphosphonates are initiated after a course of teriparatide, they enhance mineralization of the newly formed and less mineralized bone produced by the action of teriparatide on osteoblasts (Kurland et al 2004).

Monitoring of treatment

Although dual X-ray absorptiometry (DXA) is considered to be the gold standard for monitoring the response to osteoporosis treatment, the best method of monitoring a patient’s response to anabolic drug treatment is still being debated. Within the first year of therapy using teriparatide, BMD typically increases at the spine and to a lesser extent at the proximal femur. Conversely, decreases in BMD may be observed in areas of predominantly cortical bone, such as the distal radius. The latter may result from a relatively greater increase in bone diameter compared with cortical thickness (Stroup et al 2008). Of note is the finding that increased lumbar spine BMD accounts for only 30%–41% of the vertebral fracture risk reduction following teriparatide therapy, suggesting that improvements in non-BMD determinants of bone strength, such as increases in bone thickness and diameter, also play an important role (Chen et al 2006). Through stimulation of bone remodeling, teriparatide could also improve bone quality by reducing the amount of microdamage, and by removing highly mineralized bone.

Despite the limitations of DXA, current recommendations regarding monitoring of teriparatide therapy suggest annual or 2-yearly DXA scans, similar to the evaluation of response to anti-catabolic agents. QCT is an attractive technique that could provide complementary information on the effects of teriparatide on bone microarchitecture and structure. However, the lack of availability, high radiation exposure and high coefficient of variation outside clinical trials currently limit the use of this modality in the clinical setting. Measurement of serum markers of bone formation, particularly PINP or PICP at baseline and after 3–6 months of treatment, may provide another method of monitoring the efficacy of teriparatide treatment and help assess medication adherence (Kurland et al 2000; Eastell et al 2006). It is, however, important to remember that bone markers are subject to intra-individual variability (Ebeling and Akesson 2001) especially if not sampled correctly or when measured in routine clinical practice. Therefore, results should be interpreted with caution and take into account these possible limitations.

Patient perspective: compliance and reduction of back pain

Compliance with daily injections of teriparatide as well as patient satisfaction and acceptability of this treatment were assessed in a study of 116 men and women with osteoporosis (Adachi et al 2007). Reported compliance was excellent with 89% and 82% of the participants still taking the medication at 6 months and 18 months, respectively. Globally, patient satisfaction with teriparatide was 73% at 3 months, 77% at 6 months, and 86% at 18 months. The compliance with teriparatide in this study is similar to the one reported in clinical trials of teriparatide and is in contrast with the 50%–75% discontinuation rate observed after 1 year of oral bisphosphonate therapy (McCombs et al 2004; Cramer et al 2005). This study also demonstrates that the initial fear of injections is usually overcome after a few months of treatment and does not impede patient satisfaction.

Another advantage of teriparatide over bisphosphonates is the reduction of back pain. A meta-analysis comprising 4 randomized and controlled trials, of which 1 was performed in men with idiopathic or hypogonadal osteoporosis (Orwoll et al 2003), showed that severe back pain was reduced by 61% in the pooled teriparatide vs the pooled comparators trials (placebo, alendronate, or hormonotherapy) (Nevitt et al 2006). The risk reduction for any back pain was evident after only 6 months of teriparatide. In particular, the results were not different across trials, supporting a similar effect in both men and women. This study also suggests that the beneficial effect of teriparatide on back pain may be explained by a reduction in vertebral fractures.

Conclusion

Reduced bone formation with resulting thinning of trabecular bone in excess of cortical bone in men with osteoporosis makes teriparatide an especially attractive treatment for men. However, until further studies demonstrate its efficacy on reducing non-vertebral and hip fractures and the cost of teriparatide is reduced, teriparatide should be
restricted to patients at high risk of an osteoporotic fracture, who are unable to tolerate anti-catabolic therapy, or who have worsening BMD or persistently low BMD, or suffer fractures while receiving anti-catabolic therapy (Stroup et al 2008).

Disclosures
The authors have no conflicts of interest to declare.

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