Established in 1871
Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Review article | Published 4 June 2014, doi:10.4414/smw.2014.13952
Cite this as: Swiss Med Wkly. 2014;144:w13952

The role of teriparatide in sequential and combination therapy of osteoporosis

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Summary

Osteoporosis is complicated by the occurrence of fragility fractures. Over past years, various treatment options have become available, mostly potent antiresorptive agents such as bisphosphonates and denosumab. However, antiresorptive therapy cannot fully and rapidly restore bone mass and structure that has been lost because of increased remodelling. Alternatively recombinant human parathyroid hormone (rhPTH) analogues do increase the formation of new bone material. The bone formation stimulated by intermittent PTH analogues not only increases bone mineral density (BMD) and bone mass but also improves the microarchitecture of the skeleton, thereby reducing incidence of vertebral and nonvertebral fractures.

Teriparatide, a recombinant human PTH fragment available in Switzerland, is reimbursed as second-line treatment in postmenopausal women and men with increased fracture risk, specifically in patients with incident fractures under antiresorptive therapy or patients with glucocorticoid-induced osteoporosis and intolerance to antiresorptives. This position paper focuses on practical aspects in the management of patients on teriparatide treatment. Potential first-line indications for osteoanabolic treatment as well as the benefits and limitations of sequential and combination therapy with antiresorptive drugs are discussed.

Key words: *osteoporosis; teriparatide; fracture risk; combination therapy*

Introduction

For the treatment of osteoporotic patients two different classes of drugs are being used: antiresorptives and osteoanabolics. Parathyroid hormone ($PTH_{1–84}$;not available in Switzerland) and its fully active fragment $PTH_{1–34}$ (teriparatide) represent the only available osteoanabolic drugs for osteoporosis treatment at present. Teriparatide is a recombinant formulation of endogenous PTH, containing a 34 amino-acid sequence which is identical to the N-terminal portion of the human hormone ($rhPTH_{1–34}$) [1].

Osteoanabolic agents are an attractive therapeutic option because of their direct stimulation of bone formation, an action not shared by any current antiresorptive drug. The bone formation induced by PTH analogues not only increases bone mineral density (BMD) and bone mass but also improves the microarchitecture of the skeleton, thereby leading to improved bone strength and increased mechanical resistance. Controlled trials have shown that $PTH_{1–34}$ significantly reduces the incidence of vertebral and nonvertebral fractures [1, 2]. The beneficial effect of teriparatide on hip fracture incidence, however, remains unknown as the study by Neer et al. was not sufficiently powered to address site-specific incidence of nonvertebral fractures [2]. A current concept regarding the mode of action of teriparatide is related to its ability to stimulate processes associated with bone formation before it stimulates processes associated with bone resorption. This sequence of events has led to the concept of the anabolic window, the period of time when teriparatide is maximally anabolic [3].

In Switzerland, teriparatide is reimbursed as second-line treatment in postmenopausal women and men with osteoporosis and increased fracture risk, specifically in patients with incident vertebral fracture during treatment with antiresorptive drugs. Furthermore, teriparatide is approved for the treatment of adults with glucocorticoid-induced osteoporosis (GIOP) and increased fracture risk if antiresorptives are not tolerated or contraindicated.

After a first position paper on the indication for teriparatide treatment in Switzerland published in 2011 in this journal [4], a panel of Swiss internists, endocrinologists and rheumatologists specialised in the treatment of osteoporosis (who also coauthored this position paper) met in March 2013 to discuss the following research questions regarding the use of teriparatide in clinical practice:

– What is the definition of treatment failure in osteoporosis (i.e., when should teriparatide be prescribed as second-line therapy)?

– Alternatively, which patients would benefit from first-line treatment with an osteoanabolic drug?
– What are the benefits and limitations of the use of teriparatide as (a) sequential therapy in patients with prior antiresorptive treatment, (b) as add-on (combination) to prior antiresorptive therapy, and (c) as a *de-novo* combination therapy in previously untreated patients?

Treatment failure in osteoporosis

The efficacy of an antiresorptive treatment in osteoporosis is based on the demonstration of a reduction in the incidence of new fractures supported by a significant increase in BMD and a decrease in bone turnover markers. Specifically for an individual patient the question arises whether therapeutic agents, such as bisphosphonates, are effective once nonadherence is excluded. As observed in placebo-controlled trials, fractures occur in both placebo and actively treated patients. An effective intervention decreases the risk of fracture but does not eliminate the risk. Usually risk reductions are in the range of 30%–70% for vertebral fractures, 40%–50% for hip fractures and 15%–25% for nonvertebral fractures [5, 6]. Thus fractures alone during the course of treatment cannot be taken as proof of treatment failure [7]. Furthermore, the use of intermediate endpoints / surrogate measures to evaluate improvements in bone strength does not necessarily well correlate with fracture risk reduction. Hence, the relationship between change in BMD and fracture risk is not linear and is affected differently by the various antiresorptives, whether oral or intravenous bisphosphonates or subcutaneous denosumab [8–11]. Hence, changes in BMD alone do not explain the antifracture efficacy of treatment: some patients with unchanged or even decreased BMD may still have some decrease in fracture risk [12].

Recently, a working group of the Committee of Scientific Advisors of the International Osteoporosis Foundation (IOF) published a set of criteria to define failure to respond to antiosteoporotic treatment [7]. If nonadherence and occult causes of secondary osteoporosis are excluded, the following circumstances have been proposed to define treatment failure: (a) two or more incident fragility fractures, (b) one incident fracture and elevated bone turnover markers at baseline with no significant reduction during treatment (with an antiresorptive), a significant decrease in BMD, or both, and (c) both no significant decrease in bone markers and a significant decrease in BMD. Significant changes in surrogate markers as an indicator of failure to respond to treatment are defined as decrease in bone markers less than the least significant change (LSC; for bone resorption markers this corresponds to a decrease of less than 20%–30% from baseline) and a decrease in BMD greater than the LSC (for BMD this corresponds to a decrease of more than 4%–5% from baseline) (table 1).

Accordingly, teriparatide could be indicated to replace an antiresorptive drug not only in presence of a new vertebral fracture, but under any of those circumstances. However we recognise that the proposed definition of treatment failure (above) is not strongly evidence based. On another side, randomised controlled trials of teriparatide have shown fracture risk reduction in a large range of patients, independent of their baseline risk.

Potential use of teriparatide as first-line treatment option

The need for daily self-injection and the much higher cost compared with other forms of treatment limit the widespread use of PTH analogues. In most countries, PTH therapy is indicated for treatment in severe osteoporosis. Specifically, in Switzerland $PTH_{1–34}$ (teriparatide) is reimbursed in men and postmenopausal women who continue to fracture (vertebral fractures only) despite adequate antiresorptive treatment and in patients with GIOP and intolerance or contraindications to bisphosphonates (second-line treatment). Although the safety and efficacy of teriparatide have been studied beyond 2 years of treatment, the generally approved duration of therapy is limited to 2 years [13]. Therapy with antiresorptive agents causes refilling of the remodelling space, an increase in secondary mineralisation and stabilisation of bone architecture, which improves bone strength and thereby reduces the incidence of fractures. However, antiresorptive therapy is unlikely to rebuild bone structure that has been lost as a result of increased bone remodelling. Moreover, in patients with advanced osteoporosis, in whom considerable thinning of the trabecular network has already taken place, the antifracture efficacy of antiresorptives may be limited [14]. Hence, owing to their ability to increase the production of new bone via direct and indirect anabolic effects on osteoblasts [15], rhPTH analogues may offer a unique treatment alternative in patients with advanced osteoporosis. As such, potential candidates for *first-line treatment* with teriparatide include patients with severe osteoporosis and high fracture risk. We suggest a definition of patients with high fracture risk including those with (a) a low BMD (T-score <−2.5 standard deviations [SD]) and prevalent vertebral fractures or major nonvertebral fragility fractures, (b) patients with a very low T-score of ≤−3.5 SD (in absence of fragility fractures or other risk factors), and (c) patients with a low BMD (T-score <−3 SD) and additional risk factors, including advanced age and glucocorticoid therapy (table 2). A major effect of glucocorticoids on the skeleton is a decrease in bone formation and unchanged or enhanced bone resorption. General current guidelines recommend bisphosphonates as first-line agents in the prevention and treatment of GIOP, but as reduction of osteoblast function is a major determinant of GIOP, it appears logical to consider treatment with a bone-forming agent. It has been shown that teriparatide is an effective treatment of GIOP. In a randomised, double-blind trial, patients with GIOP were treated

Table 1: Circumstances defining treatment failure in patients on antiresorptive therapy.

Occurrence of – two or more incident fragility fractures – one incident fracture and elevated bone turnover markers at baseline with no significant reduction during treatment, a significant decrease in BMD, or both – no significant decrease in bone markers and a significant decrease in BMD
BMD = bone mineral density

with teriparatide or alendronate for 36 months [16]. This trial confirmed the favourable effects of rhPTH (greater increase in BMD and lower incidence of vertebral fractures than with alendronate) which had already been demonstrated in an 18-months trial [17].

A special group of patients for whom first-line teriparatide could also be beneficial is men and women with idiopathic osteoporosis – bone fragility at a younger age and after exclusion of a secondary cause [18]. The most consistent abnormalities noted in men with idiopathic osteoporosis are decreased sex hormone levels (due to an increase in serum sex hormone-binding globulin) as well as decreased circulating insulin-like growth factor-1 (IGF-1) levels, which may contribute to impaired bone formation [19]. Hence, anabolic agents may correct the underlying defect in osteoblast function [20]. Trials show that daily subcutaneous administration of teriparatide increases BMD of the spine and femoral neck [21] and decreases vertebral fracture risk [22] in men with osteoporosis.

Sequential and combination therapy with rhPTH

Recent data on the effect of sequential and combination therapy with osteoanabolic and antiresorptive drugs are of importance.

We addressed the following questions regarding sequential and combination therapies:

– Is there an influence of previous antiresorptive treatment on subsequent response to rhPTH?
– In patients previously treated with antiresorptives, is it better to add teriparatide or to switch to teriparatide alone?
– Because teriparatide is approved only for 2 years of treatment, is it necessary to follow this treatment course with an antiresorptive drug?
– In treatment-naïve patients, can one use simultaneously *de-novo* osteoanabolic and antiresorptive agents in a manner that will expand the anabolic window?

Sequential therapy

Owing to its use as second-line treatment in women and men with increased fracture risk, most patients who commence teriparatide treatment have previously received antiresorptive drugs. There are several studies investigating the sequential strategy, i.e. *switching* from an antiresorptive drug such as oral bisphosphonates or raloxifene to rhPTH [23–26]. In the OPTAMISE study patients on bisphosphonate (risedronate or alendronate) therapy for at least 2 years where switched to daily $PTH_{1–34}$ for 1 year [24, 27–29]. Significant differences in serum levels of the bone formation marker procollagen type 1 amino-terminal propeptide (P1NP) between previously risedronate- and alendronate-treated patients were seen as soon as 1 month, with a more pronounced response to teriparatide in patients previously treated with risedronate as compared with alendronate. Lumbar spine BMD showed significant differences in percentage changes from baseline between prior bisphosphonate groups after one year. The more pronounced effect on BMD in patients previously treated with risedronate may be explained by the differences in binding affinities between risedronate and alendronate. At the total hip, quantitative computed tomography (QCT) showed that there was a greater increase in the volumetric trabecular BMD in patients pretreated with risedronate. However, as the integral total hip volumetric BMD did not change, concomitant loss in cortical bone mass has to be assumed.

The prospective, randomised open-label EUROFORS study included women with advanced postmenopausal osteoporosis (mean spine T-score –3.3 SD and at least one vertebral or nonvertebral fracture) who had no previous bisphosphonate treatment (n = 84) and those who had been treated with bisphosphonates prior to teriparatide (n = 419) [16, 21]. A subgroup of the previously treated patients was classified as therapy failure (n = 285), defined either clinically as occurrence of a fracture or according to densitometry as inadequate increase in BMD despite continued treatment for a median 54 months. A continued, significant increase in lumbar spine and hip BMD was observed over the 24-month period of treatment with the highest values seen after 2 years. The mineral content at the lumbar spine increased by 10.5% ($p < 0.001$) in the entire group and by 9.8% in patients with an inadequate effect of previous bisphosphonate therapy ($p < 0.001$). Graeff et al. used finite element analysis-based strength measures on 44 patients out of the EUROFORS population to monitor teriparatide effects on whole bone and local fracture risk [30]. Finite element analysis-based strength and stiffness calculations for three different load cases (compression, bending, and combined compression and bending) were compared with volumetric BMD and apparent bone volume fraction, as well as dual-energy X-ray absorptiometry-based areal BMD of the lumbar spine. Highly significant improvements in all analysed variables as early as 6 months after starting teriparatide were found. Treatment with teriparatide led to bone strength increases for different loading conditions of close to 30%. Borggrefe et al. studied the changes in bone distribution, geometry, and bone strength based on three-dimensional QCT of the femoral neck in 52 subjects receiving teriparatide during the EUROFORS study [31]. They showed that the cortical area started to increase after 12 months and showed a significant increase of 4.4% compared with baseline after 24 months of treatment ($p < 0.01$). Since there was no increase in total area, this finding can be interpreted as the result of apposition at the endosteal surface. Overall, in the course of treatment no significant differences between the subgroups with or without prior antiresorptive treatment could be detected. Thus, rhPTH treatment is effective in increasing bone formation, BMD and bone strength after prior long-term exposure to antiresorptive therapies. In addition, the EUROFORS and other studies demonstrate that duration of previous antiresorptive therapy and time between stopping

Table 2: Potential candidates for first-line treatment with teriparatide.

Patients with high fracture risk, including – Low BMD (T-score <−2.5 SD) and prevalent vertebral (≥2 vertebral fractures, Genant grade 2 and 3) or hip fracture – Low BMD (T-score <−3.0 SD) and additional risk factors (i.e., advanced age, glucocorticoid treatment) – Low BMD (T-score <−3.5 SD)
BMD = bone mineral density; SD = standard deviation

previous therapy and starting teriparatide did not affect the BMD response at any skeletal site [32, 33].

Another approach in sequential therapy would be *adding* rhPTH therapy to on-going antiresorptive treatment. Lindsay et al showed that, in postmenopausal women, adding teriparatide to on-going hormone replacement therapy resulted in a superior gain in BMD compared with women continuing oestrogen supplementation only [34]. Similarly, Cosman et al. found that adding $PTH_{1–34}$ to alendronate was also associated with increases in BMD above the effect of alendronate alone [35].

In a randomised open-label study, Cosman et al. compared the effect of *switching versus adding* to teriparatide in postmenopausal women on treatment with either raloxifene or alendronate for at least 18 months [26]. Interestingly, the response to teriparatide differed depending on whether the prior antiresorptive agent was continued or stopped. The biochemical bone turnover response to teriparatide was reduced in add versus switch patients. In contrast, the bone density responses were greater in add versus switch patients in both spine and hip in the alendronate group and in the hip in the raloxifene group. This superior effect on BMD with the add regimen might be due to the fact that, although absolute increase in bone markers were lower with the add regimen, the anabolic window (the difference between increases in bone formation over bone resorption) was greater with the add regimen [32]. However, whether regimens of switching to, as opposed to adding, teriparatide results in a significant effect on fracture risk reduction remains to be determined.

Finally, observational studies suggest that BMD decreases more or less rapidly in individuals who do not take antiresorptive agents after cessation of rhPTH, whereas antiresorptive therapy after rhPTH treatment can maintain or enhance rhPTH-induced BMD gain further [22, 36–39]. In a controlled trial, patients with osteoporosis treated for 1 year with $PTH_{1–84}$ were subsequently randomly allocated to receive alendronate or placebo for an additional year [40]. Over 2 years, women who received alendronate after $PTH_{1–84}$ therapy had significant increases in spine BMD of 12.1% compared with 4.1% in women treated with placebo after PTH treatment. BMD at the hip was increased above baseline in all groups except those receiving PTH followed by placebo. Following $PTH_{1–84}$ therapy with alendronate consolidated the gains in bone mass obtained during treatment with $PTH_{1–84}$ alone. Hence, sequential therapy, with bisphosphonate therapy after rhPTH treatment, is mandatory although the benefits in terms of fracture risk reduction remain speculative [1].

Combination therapy

In the Parathyroid Hormone and Alendronate (PATH) study, 238 postmenopausal women with low BMD were randomly assigned to daily treatment with $PTH_{1–84}$, alendronate or both for 12 months [41]. The areal BMD at the spine increased in all treatment groups and did not differ significantly between the $PTH_{1–84}$ and the $PTH_{1–84}$ plus alendronate group. P1NP increased markedly in the $PTH_{1–84}$ group but not in the combination therapy group, which does not suggest a synergy between PTH and alendronate. The volumetric density of trabecular bone at the spine increased more with parathyroid hormone alone than with combination therapy or alendronate alone. In the PTH group, the volumetric density of cortical bone decreased, an effect prevented by the combination treatment with alendronate, indicating that alendronate might counteract effects of PTH on cortical porosity [41]. The observed increase in cortical volume therefore might predominantly be due to trabecularisation on the endocortical bone surface.

These results support those observed in men treated with alendronate, $PTH_{1–34}$ or both [42]. Alendronate therapy was given for 30 months, and teriparatide was started after the first 6 months. BMD of the lumbar spine and femoral neck increased significantly more in men treated with $PTH_{1–34}$ alone than in those in the other two groups.

In contrast to these studies using oral bisphosphonates, divergent effects in combination regimens using parenteral zoledronate or denosumab have been observed. In a randomised, partially double-blind trial, Cosman et al. investigated the effects of combination therapy with a single infusion of zoledronic acid and daily $PTH_{1–34}$ versus either agent alone on BMD and bone turnover markers [43]. In the combination group, spine BMD increased more rapidly than with either agent alone. Moreover, the combination therapy increased total hip BMD more than the monotherapies after 13 weeks, with final increments of 2.3%, 1.1% and 2.2% at 1 year in the combination, $PTH_{1–34}$ and zoledronic acid groups, respectively. The study is limited by its short duration and insufficient power for fracture outcomes.

Interestingly, bone turnover markers decreased rapidly, but only transiently (<6 months), when teriparatide was combined with a single infusion of zoledronic acid. This finding is in contrast to studies using oral bisphosphonates daily (alendronate 10 mg) [41, 42], which resulted in a sustained reduction in bone turnover markers, and might explain differences in initial gain in BMD across the studies. Recently, a similar approach has been investigated using $PTH_{1–34}$ in combination with denosumab (60 mg subcutaneously 6–monthly) versus either drug alone [44]. The combination of teriparatide and denosumab led to a significantly larger increase in spine and hip BMD after 6 and 12 months as compared with either drug alone.

In summary, the effects of combination strategies seem to depend on the type of antiresorptive and its mode of administration – that is, they depend on the pharmacodynamic profile of the drug – with potentially superior additive effects of teriparatide when combined with zoledronic acid or denosumab. Nevertheless and specifically as long as fracture endpoint data are lacking, any possible benefits of combination therapy must be weighed against the additional costs and inconveniences of taking two drugs rather than one.

Implications for the use of teriparatide in clinical practice

As osteoporosis is mostly due to bone loss, antiresorptive therapy, mainly bisphosphonates, are a cornerstone of therapy. However, as a result of their different mode of action, anabolic drugs have increased our options in the treatment of osteoporosis. Postmenopausal women and men with

severe and progressive osteoporosis despite antiresorptive therapy ("treatment failure", see above) as well as patients with GIOP need to be evaluated for a treatment course with osteoanabolic drugs. At present, only teriparatide (Forsteo®, 20 µg subcutaneously) is available in Switzerland. However, in future anabolic alternatives (such as anti-sclerostin antibodies) might become available. Teriparatide is reimbursed for second-line treatment for a treatment course of 24 months. Afterwards, sequential therapy with an antiresorptive drug following teriparatide to maintain increases in bone mass and support secondary mineralisation of newly formed bone is strongly recommended.

In clinical practice most patients are pretreated with antiresorptive agents before starting teriparatide. According to the current evidence, switching to teriparatide or combining it with an antiresorptive therapy seems to provide additional benefits regarding different intermediate parameters of skeletal integrity such as BMD, bone strength and stiffness. However, it must be noted that, regarding the use of combined or sequential therapy, no trial exists with fracture as primary endpoint, and we are thus only referring to surrogate markers of bone health. The OPTAMISE and EUROFORS trials showed that prior antiresorptive treatment only modestly blunted the BMD response to teriparatide. Any delay due to previous antiresorptive therapy, if present, is overcome in terms of patient response to therapy [32].

Overall, it remains unclear as to how and whether combination or sequential therapy approaches can be used in a manner that has advantages over rhPTH monotherapy. Recent data on the effect of treatment regimens using teriparatide in combination with zoledronic acid or denosumab, however, are noteworthy. It seems that combination therapies with intravenous or subcutaneous antiresorptive drugs result in only transient suppression of bone remodelling, as mirrored by transient decreases in bone turnover markers. This might explain the more rapid and/or more pronounced increase in BMD as compared with studies using oral bisphosphonates (alendronate 10 mg daily). Whether the use of weekly or monthly oral bisphosphonates in combination with rhPTH also would attenuate an anabolic window and, ultimately bone gain, is unknown.

In our opinion, patients with severe osteoporosis and high fracture risk, including patients with multiple vertebral fractures or very low BMD, could also be considered for first-line osteoanabolic treatment. For these purposes and for combination treatments, however, approval by health insurers needs to be obtained prior to treatment, as the use of teriparatide in Switzerland remains currently limited.

Funding / potential competing interests: This paper is based on discussions held during a meeting sponsored by Eli Lilly (Switzerland). None of the authors have received any financial support or paid fee for the writing of this review.

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