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Editorial

How different is the once-weekly teriparatide from the daily one or the same?

Teriparatide is a N-terminal fragment (1-34 amino acids) of parathyroid hormone (PTH) that can bind parathyroid hormone receptor type 1, PTH1R, to activate it similarly to the full-length (1-84 amino acids) hormone. Daily subcutaneous injection of teriparatide has been globally available as an anabolic therapy for severe osteoporosis since early 21st century. Once-weekly subcutaneous injection of teriparatide, 56.5 μg/injection instead of 20 μg for daily teriparatide injection, as an alternative therapeutic regimen was developed and approved in late 2013 in Japan. At this moment, once-weekly teriparatide is available in Japan and South Korea. Two independent papers focusing on once-weekly teriparatide in daily clinical practice are published in this issue of *Osteoporosis and Sarcopenia* [1,2]. Both of them have demonstrated that bone resorption markers did not increase with once-weekly teriparatide injections [1,2]. Changes of serum levels of N-terminal propeptide of type I procollagen (P1NP) as a bone formation marker were equivocal during the treatment, even though bone mineral density was consistently increased [1,2]. It might be unique in the once-weekly teriparatide, because teriparatide is known as a bone anabolic agent that stimulates bone metabolism, especially bone formation.

Efficacy and safety of once-weekly teriparatide has been established in the Teriparatide Once-Weekly Efficacy Research (TOWER) study as a randomized double-blind placebo-controlled phase 3 trial for 72 weeks in patients with primary osteoporosis with high fracture risk [3]. Once-weekly injections of teriparatide reduced the risk of new vertebral fracture with a cumulative incidence of 3.1% in the teriparatide group, compared with 14.5% in the placebo group, and a relative risk of 0.20 (95% confidence interval, 0.09 to 0.45) [3]. At 72-week, teriparatide administration increased bone mineral density by 6.4%, 3.0%, and 2.3% at the lumbar spine, the total hip, and the femoral neck, respectively, compared with the placebo [3]. The risk reduction of new vertebral fracture with once-weekly teriparatide seemed not to be inferior to that with its daily injection [4], even though the amount of weekly administered teriparatide was 56.5 μg for once-weekly injection being much less than 140 μg a week for daily injection therapy.

The once-weekly teriparatide is now clinically available as an alternative option for an anabolic therapy for osteoporosis. The question is how different is once-weekly teriparatide from its daily administration. First of all, once-weekly administration is more convenient to some patients than the once daily injection. More importantly, mechanisms for anabolic effects of once-weekly teriparatide could be somewhat different from those of its daily injection. The most remarkable difference is apparently their effects on bone metabolic markers. Serum levels of bone formation markers, especially P1NP, increase with daily administration of teriparatide no later than 1 month after the first injection, followed by the increase in bone resorption markers, such as type I collagen cross-linked C-telopeptides (CTX) [5]. Afterward their increases hold at least for a year. This profile of changes in bone metabolic markers, formation first followed by resorption, during daily injections of teriparatide provides an “anabolic window” that is temporally open for accumulation of a significant amount of new bone [6]. In contrast, once-weekly teriparatide has no effects on urinary excretion of type I collagen cross-linked N-telopeptide (NTX) as a bone resorption marker during early treatment period even followed by its decrease at 48-week of treatment and thereafter [3]. It only transiently elevates serum P1NP until 12-week of treatment [3]. Accordingly, once-weekly teriparatide also might open the “anabolic window” with the temporal increase in bone formation without the increase in bone resorption. If this is the case, it is interesting to note that the mechanism to open the “anabolic window” is different among two protocols of administration of teriparatide. Data shown in the paper reported by Omura [1] and that by Ifuku et al. [2] might be in line with those in the phase 2 clinical trial [3], although data of bone metabolic markers before 24 weeks of the treatment were not available in either report.

Temporal profile of changes in bone metabolic markers with a single administration of 56.5 μg of teriparatide have been investigated in human in more detail [7]. Exogenously administered teriparatide was detected in circulating blood only for 4–6 hrs with a reciprocal decrease in serum intact PTH at least until 24 hrs after its subcutaneous injection [7]. Accordingly, urinary excretion of NTX and serum P1NP only transiently increased and decreased for 8 hrs, respectively, followed by reaching serum P1NP level higher than its baseline value 24 hours after administration of teriparatide [7]. Serum P1NP levels and urinary excretion of NTX were continuously higher and lower than their baseline values, respectively, for 14 days after the injection [7]. These data suggest that the exogenous single administration of teriparatide temporally and transiently activates bone resorption and subsequently stimulates bone forming osteoblastic activity. Since bone metabolic markers are measured in samples obtained just before its administration in long-term clinical trials of teriparatide, an increase in P1NP and no change or a decrease in NTX during treatment with once-weekly teriparatide has been reported [3]. Therefore, once-weekly teriparatide could build new bone through transient

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activation of bone remodeling.

Frequency of administration may be important to build a strong bone with teriparatide. A pivotal physiological role of PTH is to mobilize calcium from bone to circulation to maintain serum calcium level constant. Continuous elevation of circulating PTH levels in primary hyperparathyroidism induces bone loss along with hypercalcemia. In contrast, as for treatment of osteoporosis, an essential pharmacological action of exogenous PTH is to increase the number of cells in an osteoblast lineage to stimulate bone formation. The anabolic action of exogenous PTH should overcome its effect on bone resorption, although it is only transient. Intermittent administration of PTH makes such a clinically favorable effect on bone possible. Daily injections of teriparatide provide an enormous anabolic effect on trabecular bone but much less on cortical bone, such as shaft of radius [4]. Some preclinical and clinical data have suggested that once a day teriparatide injections increase cortical porosity in long bones [8,9]. Accumulating evidence of preclinical data demonstrates that less frequent administration could decrease cortical porosity induced by exogenous teriparatide [8,10]. Quantitative computed tomography data indicated that cortical thickness and cortical cross sectional area of femoral shaft was significantly increased with treatment for 72 weeks with once-weekly teriparatide compared with placebo [11], suggesting its favorable effects on cortical bone during the treatment period, although effects of once-weekly teriparatide on cortical porosity in human is not yet available.

Romosozumab, anti-sclerositin antibody, is another bone anabolic agent. It is now clinically available in Japan and United States, and is expected to become approved soon in many other countries. Romosozumab not only stimulates bone formation but inhibits bone resorption simultaneously [12]. Its effects on bone mineral density are robust. The increase in bone mineral density with monthly romosozumab was significantly higher than that with daily administration of teriparatide [12]. Overall changes in bone metabolic markers through romosozumab treatment are somewhat similar to those in once-weekly teriparatide. However, anabolic effects of romosozumab are based on bone modeling without activation of resorption, whereas those of once-weekly teriparatide come along with bone remodeling following rapid, transient but cyclic activation of bone resorption. Taken together, once-weekly teriparatide at a dose of 56.5 μg may be a distinctive and unique anti-osteoporosis agent and provide another option of remodeling-based anabolic treatments in patients with osteoporosis.

Conflicts of interest

Yasuhiro Takeuchi received research grants from Chugai Pharmaceutical, Daiichi-Sankyo and Teijin Pharma, and consulting fees from Chugai Pharmaceutical, Daiichi-Sankyo, Asahi Kasei Pharma, Teijin Pharma, Astellas, and Amgen Astellas Biopharma. **ORCID**. Yasuhiro Takeuchi: 0000-0002-0847-5233.

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