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COMMENTARIES

Teriparatide: Variations on the Theme of a 2-Year Therapeutic Course

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Commentary on: Cosman F, Wermers RA, Recknor C, Mauck KF, Xie L, Glass EV, Krege JH. Effects of teriparatide in postmenopausal women with osteoporosis on prior alendronate or raloxifene: differences between stopping and continuing the antiresorptive agent. *J Clin Endocrinol Metab*. 2009 Oct;94(10):3772-80.

Finkelstein JS, Wyland JJ, Leder BZ, Burnett-Bowie SA, Lee H, Jüppner H, Neer RM. Effects of teriparatide retreatment in osteoporotic men and women. *J Clin Endocrinol Metab*. 2009 Jul;94(7):2495-501.

Teriparatide is the first osteoanabolic drug, approved by the FDA in 2002, for the treatment of osteoporosis. It added an attractive alternative to antiresorptive bisphosphonate drugs in the therapy of individuals with advanced disease at high risk for fracture. The anabolic actions of teriparatide [recombinant human parathyroid hormone, PTH(1-34)] are accounted for, in part, by first stimulating bone formation and then by stimulating bone remodeling, the latter process invoking an increase in bone resorption. Thus, an anabolic window is established between the time that bone formation is stimulated and bone resorption increases (1-2). Part of the idea of the anabolic window is that it does not stay open for long; there is a downturn in action as evidenced by reductions in markers of bone remodeling over time. Also noteworthy is the observation that when teriparatide or the full length PTH molecule itself, PTH(1-84), is stopped, antiresorptive therapy is necessary to maintain the densitometric gains achieved during the course of therapy (3-4). These points are consistent with current clinical practice to use teriparatide at the approved daily dose (20 µg subcutaneously) for 18-24 months. Treatment is then followed by an antiresorptive agent, like a bisphosphonate (1;4). The dialogue related to osteoanabolic therapy has entered a new era marked by questions that are pertinent to real-life decision-making situations. Given the fact that most patients who are going to be treated with teriparatide or PTH(1-84) have been treated previously with an antiresorptive agent, is it better to *add* the osteoanabolic agent to the ongoing antiresorptive regimen or is it better to *switch* from the antiresorptive to the osteoanabolic alone? This question is addressed by Cosman *et al*. (5) in the October issue of *JCEM*. The study by Finkelstein *et al*. (6) in the July issue of *JCEM* deals with another pertinent clinical question about retreatment with teriparatide after subjects have received the full 24 months of therapy. Will retreatment after a 12-month period off therapy lead to similar gains achieved during the first course of therapy? Both studies add important information to our understanding of teriparatide's actions in the context of clinical care.

The cohort studied by Cosman *et al*. had been treated previously for at least 18 months with raloxifene or alendronate. This was followed by an 18-month period of therapy with teriparatide either alone (*switch*) or with the antiresorptive drug

continued (*add*). While the increase in bone turnover markers was greater when patients were *switched* from either alendronate or raloxifene to teriparatide, the densitometric gains by DXA were greatest when teriparatide was *added* to the antiresorptive drug. It is not intuitively obvious why this might be the case. But careful inspection of Figure 2 of their article gives a clue. When teriparatide was *added* to alendronate or raloxifene, even though ultimate changes in bone turnover markers were lower than in the context of *switching* from the antiresorptive to teriparatide, the anabolic window was much greater under *adding* conditions. In the *add* arm, the increase in levels of the bone formation marker, P1NP, is virtually maximal by the 1-month time point while the subsequent increase in the bone resorption marker, CTX, is sluggish, not reaching its peak until 12 months. On the other hand, subjects in the *switch* arm demonstrate parallel increases in the kinetics of both P1NP and CTX, each marker reaching its peak level between 3 and 6 months. Thus there is not much of an anabolic window created in the *switch* arm of the study, despite the fact that the activity of the markers is higher than in the *add* arm. The more substantial gains in BMD when teriparatide is *added* to alendronate or raloxifene can be explained in this manner. If changes in BMD correlate with a better outcome vis-à-vis fracture risk, then one could be more inclined to continue the antiresorptive agent in this clinical setting. However, the study had too few subjects, and fractures were not an endpoint, so one cannot come to any definitive conclusions in this regard.

Another interesting aspect of this study, but not highlighted, is that the increases in bone turnover markers and bone density at the lumbar spine were greatest after raloxifene than after alendronate, a finding consistent with a previous study by Ettinger *et al*. (7). The antiresorptive agent that has the lesser effect on bone turnover seems to be associated with the more exuberant subsequent effect on bone markers and bone density induced by teriparatide. Similar observations have been made by Miller *et al*. (8).

The study by Finkelstein *et al*. (6) was a planned continuation of their randomized trial comparing the effects of alendronate, teriparatide, or both on BMD and bone turnover in men and women with low BMD (6;9). In contrast to the study from Cosman *et al*., subjects had not previously been treated for osteoporosis. The results of the first phase of their study published previously (9) are consistent with the studies of Black *et al*. (10) using PTH(1-84). In both cases, the combination arm of osteoanabolic and alendronate therapy together did not provide as great a change in BMD in the lumbar spine as did monotherapy with the osteoanabolic agent alone. In the current study by Finkelstein *et al*., participants who completed this first phase of the trial were then monitored for 12 months after teriparatide was withdrawn and then retreatment with teriparatide was instituted for 12 months. Although the study had several other arms, data in the paper are provided only for the cohort in which teriparatide was used alone for 2 years, followed by 1 year of no therapy, followed by 1 year of teriparatide retreatment. During the period off teriparatide, not surprisingly, bone turnover markers and bone density at the lumbar spine fell. When subjects were retreated with teriparatide, the losses in BMD experienced during the period off therapy were recovered such that subjects' BMD gains were restored to levels they had achieved during the first period of teriparatide therapy. The authors argue that this is an attenuation of teriparatide responsiveness because the quantitative gains were not as great as the gains during the first period of teriparatide therapy. However, the slope of the rise in BMD during the retreatment period appears to be virtually identical to the slope of the increase during the initial period, raising the possibility that if treatment had been continued beyond the first retreatment year, gains would have been even greater. Arguing, however, as they do that this represents an attenuation of the response to teriparatide, it is noteworthy that bone turnover markers start to fall rather dramatically after only 1 year of initial therapy. This is somewhat surprising and may indicate that in this experimental paradigm, in which a higher average dose of

teriparatide was used than in most other studies (*i.e*., 37 µg vs. 20 µg), the duration of the anabolic window was shorter. Maybe higher doses of teriparatide are associated with an earlier attenuation of effect. A recent study by Cosman *et al*. suggests that against a backdrop of continuous alendronate therapy, a 12-month hiatus between two courses of teriparatide therapy is associated with similar increases in BMD and bone turnover markers when both therapeutic time periods are compared to each other (11).

These two papers, combined with other recent reports, indicate that we do not know how best to use teriparatide therapy. Options include standard approaches with a 2-year course of therapy followed by an antiresorptive agent. Whether one would consider retreating with teriparatide is still open for discussion and further study as are other possibilities such as prolonging treatment as long as bone turnover markers are still at their peak or employing teriparatide for shorter periods of time and then retreating subjects. It is also not clear whether subjects who have been on antiresorptive therapy do better if it is continued when teriparatide is started. The studies by Cosman *et al*. (5) and Finkelstein *et al*. (6) are helping us gain greater understanding of these major clinical questions, but we don't yet have the answers.

Conflict of interest: Dr. Bilezikian reports that he is a consultant for Eli Lilly, NPS Pharmaceuticals, Merck, the Alliance for Better Bone Health, GSK, Novartis, and Amgen, and receives research support from NPS Pharmaceuticals and GSK. Dr. Cusano: none reported.

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