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COMMENTARY

Abaloparatide: a new anabolic therapy on the horizon

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Teriparatide administered by daily subcutaneous injection, was approved in the United States in 2002, and has been the only anabolic medication available in the United States for almost 13 years. Outside the US, teriparatide is joined only by intact PTH (1–84) as anabolic therapy for osteoporosis treatment. Although both anabolic and antiresorptive medications improve bone density and strength, their mechanisms of action are distinctly different.[1,2] Because anabolic agents stimulate new bone formation, they have the potential to repair disordered bone architecture and increase bone mass to a greater extent than antiresorptive therapies. Some of the anabolic action of teriparatide is through modeling on the quiescent bone surface owing to activation of resting lining cells and/or recruitment of newly formed/differentiated osteoblasts to the bone surface.[3–6] Some of the anabolic action is remodeling based, with stimulation of osteoblast activity within existing or new remodeling units, leading to overfilling of resorption cavities and, thereby, thicker packets of new bone. Larger packets of new bone growth are also seen because of the formation overspilling the already filled resorption cavities and/or stimulation of modeling–based bone formation adjacent to the remodeling cavities. The balance between the amount of modeling versus remodeling-based bone formation might change with time on teriparatide treatment.

One of the challenges with teriparatide has been the lack of appreciable difference in nonvertebral fracture incidence before at least 9 months of teriparatide treatment. Ultimately, within 18 months, teriparatide does produce a 35–50% reduction in nonvertebral fractures (range based on different definitions of nonvertebral fractures).[7] However, it is unclear if this effect is truly better than potent antiresorptive therapy in skeletal sites that are primarily cortical bone. Teriparatide does improve cortical thickness at 18–36 months,[8,9] however, BMD of the hip does not increase more with teriparatide than with alendronate.[10] Furthermore, hip strength increases modestly and not significantly more than with alendronate.[11] In the few small studies where teriparatide was compared head-to-head with bisphosphonates, whereas teriparatide reduced the risk of vertebral fractures more than alendronate[12] or risedronate,[13] nonvertebral fracture incidence did not differ between teriparatide and oral bisphosphonates. Of course, these studies were not designed or powered to assess the fracture outcomes for either vertebral or nonvertebral sites. Lastly, in patients who have already been treated with prior oral bisphosphonates or denosumab, the benefit of subsequent teriparatide treatment is diminished, particularly with respect to hip BMD[14–16] and hip strength,[17] perhaps in part because of excessive bone resorption when the stimulation of remodeling by teriparatide is coincident with the withdrawal of a potent antiresorptive agent.

A number of potential anabolic therapies have failed in various stages of development because of lack of efficacy, including several calcilytic agents designed to stimulate endogenous PTH production[18,19] and transdermal patches containing teriparatide.[20]

Abaloparatide is a synthetic analog of PTHrP that retains anabolic activity with less bone resorption, compared with PTHrP. Leder *et al.*[21] recently published results from a short term phase 2 trial of three doses of Abaloparatide (20, 40 and 80 mcg by daily subcutaneous injection), compared with daily placebo and teriparatide over 24 weeks. A small subset, 55 of the original 222 subjects, received extended treatment to 48 weeks. Enrolled subjects were largely treatment naive with no prior use of teriparatide or denosumab and no bisphoshphonate use within the previous 5 years. At 24 weeks, BMD increases above placebo were seen in the spine, total hip and femoral neck, and were for the most part dose dependent. Spine BMD increases with the two higher abaloparatide doses (40 and 80 mcg) were similar to that seen with teriparatide (5.2, 6.7 and 5.5%, respectively). In the total hip, BMD increases with the 40 and 80 mcg doses were greater than that seen with teriparatide (2.0, 2.6 and 0.5%, respectively). There were no BMD data presented for the radius. The increases in biochemical markers of bone formation (PINP and osteocalcin) stimulated by abaloparatide and teriparatide were similar, whereas the effect of abaloparatide on a marker of bone resorption (CTX) was of lesser magnitude than that seen with teriparatide.

In the small group of women who completed the extension study, spine BMD increased further from 24–48 weeks, reaching a mean increment of 12.9% with the 80 mcg abaloparatide dose.

Although the authors suggest that BMD changes appear to be linear over time, this was not clear for the hip region where BMD increments at 48 weeks were 2.1 and 2.7% for the 40 and 80 mcg doses (not different from the mean 24 weeks increments at this skeletal site). In contrast, although the magnitude of increase was smaller, total hip BMD did appear to increase further with teriparatide between 24–48 weeks. (As the subgroups are small, we should not overemphasize the importance of this. Paired data from the small group of patients who completed both 24 and 48 weeks might be more instructive than comparing the 184 women who completed the base trial at 24 weeks with the 55 women who completed the extension at 48 weeks). Nevertheless, at 24 weeks, hip BMD changes with abaoloparatide might be an important distinguishing feature between abaloparatide and teriparatide. Whether this difference persists during the latter part of a therapeutic course of these agents over 18–24 months will need to be determined. It has been shown previously that hip BMD tends to increase at a faster rate during the latter 6 months of a two-year course of treatment with teriparatide.[21] Abaloparatide injections were well tolerated without apparent safety concerns in this early trial. Incidence and severity of hypercalcemia were minimal and if anything lower than that seen with teriparatide.

Obviously the fracture data from phase 3 trials will be most important in understanding the potential clinical impact of this compound. To that end, no data have yet been published, but results of the phase 3 trial are in the public domain through recent press releases.[22–24] Both abaloparatide (80 mcg daily) and teriparatide (20 mcg daily) were similarly effective at dramatically reducing the vertebral fractures (new and worsening) compared with placebo (by 83 and 78% respectively, NSD). The results were very similar when restricted to new vertebral fractures only. Apparently abaloparatide reduced nonvertebral fracture risk by 43% ($P<0.05$) compared with a 28% reduction for teriparatide (NS). In addition, when comparing abaloparatide with placebo, there was a rapid separation of the time to first nonvertebral fracture curves. In contrast, there was no separation for teriparatide versus placebo until 420 days into the trial. Wrist fracture rate was also lower for abaloparatide (0.5%) compared with teriparatide (2.0%; group difference $P<0.015$). Consistent with the phase 2 trial, BMD changes in the hip were greater at 12 and 18 months with abaloparatide versus teriparatide and incidence of hypercalcemia was lower.

Of course, the phase 3 study findings have to be scrutinized by peer review, but they suggest that abaloparatide might be a viable anabolic agent as first-line therapy for the treatment of osteoporosis. A more modest stimulation of remodeling might prevent increases in cortical porosity and result in a more rapid improvement in cortical bone strength (with a larger and faster reduction in nonvertebral fracture) than our current lone anabolic agent. It will be important to see evidence of this effect on iliac crest histomorphometry and confirmation of this possible difference with noninvasive tests of bone strength, such as finite element analysis, particularly for the hip. It will also be important to determine what happens with administration of abaloparatide after potent antiresorptive therapy such as denosumab or bisphosphonates. A lesser degree of remodeling stimulation in this setting might address the needs of a large group of patients for whom anabolic treatment is warranted.

Conflict of Interest

Dr Cosman is an advisor for Eli Lilly, Merck and Radius, and is a speaker for Eli Lilly.

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