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COMMENTARY

Teriparatide delivery by indwelling MicroChip

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Parathyroid hormone (PTH) therapy (teriparatide, Forteo/Forsteo or PTH 1–84, Preos), the only approved anabolic therapy for bone, produces larger increments in bone mass (particularly in the spine) than those seen with anti-resorptive therapies. PTH treatment first stimulates bone formation through modeling (on previously quiescent surfaces and surfaces adjacent to remodeling cavities), and subsequently remodeling, where the balance remains positive for formation over resorption.[1–3] The growth of new bone with PTH permits larger packets of bone with overfilling of remodeling cavities evidenced by greater wall width.[4] This results in restoration of bone microarchitecture, including improved trabecular connectivity and enhanced cortical thickness,[4,5] in addition to substantial increases in bone mass.[6,7] Bone formation may also be induced on the outer periosteal surface,[8–12] possibly affecting bone size and geometry, with additional beneficial effects on bone strength,[8–10,13–16] though this has not been conclusively proven. Teriparatide reduces the risk of fractures throughout the skeleton, without regard to baseline bone mineral density (BMD) or patient age.[6,7] In two positive comparator clinical trials, teriparatide reduced new vertebral fracture incidence compared with alendronate in glucocorticoid-induced osteoporosis,[17] and compared with risedronate in women with back pain due to acute vertebral fractures.[18]

Good candidates for PTH are women and men who are at high risk of future osteoporosis-related fractures, including those with vertebral compression fractures (clinical or radiographic), other osteoporosis-related fractures with BMD in the osteoporosis range, or very low BMD even in the absence of fractures (T-Score below –3). PTH treatment should also be recommended for individuals who have been on prior anti-resorptive agents, and who have had a suboptimal response to treatment, defined as incident fractures or active bone loss during therapy, or who have persistent osteoporosis (BMD T-Score below -3) despite therapy.

There is no doubt that the daily subcutaneous injection is a significant and common barrier to the use of PTH treatment in the managements of patients with osteoporosis. Many patients can overcome their initial aversion to daily injections, and once they begin taking teriparatide they often realize that there is little discomfort and tolerate the process extremely well. However, some patients do not persist with therapy and others never agree to try. Therefore, alternative delivery systems are sorely needed. A transdermal preparation produced positive short-term findings,[19] and oral and intranasal preparations are being explored.

Farra *et al.*[20] published results of a small pilot study, first in human use, involving a totally novel delivery system for teriparatide. The system is a programmable microchip drug-delivery device less than 5.5 cm long and 3.5 cm wide. Once implanted subcutaneously in the abdomen, the drug delivery can be remotely and wirelessly controlled. The medication is stored in microwells (10 reservoirs in each of 2 microchips in the prototype device used in the study, but up to a total of 1 year's doses could be available in the next version). Each hermetically sealed microreservoir contained a daily dose of lyophilized teriparatide (40 mcg), covered by a platinum and titanium membrane. The membranes were connected by current traces to the internal electronics, and the microchip was programmed to send an electric current to ablate the membrane overlying the appropriate microwell containing the daily teriparatide dose. Once the membrane was ruptured, the drug dose was released and rapidly dissolved into subcutaneous fluid. The next day, medication in the next microwell was released. The device was able to receive and send information about drug delivery and could be adjusted as needed by remote radio communication.[21]

Eight postmenopausal women with osteoporosis, between 65 and 70 years of age, had the prototype device implanted in abdominal subcutaneous tissue near the umbilicus, in a surgeon's office under local anesthesia, a procedure that took about 30 min. The device was left in for 8 weeks before activating drug delivery, to allow full development of the expected fibrous tissue capsule. During the third month, 20 daily doses of teriparatide were delivered via indwelling microchip device. Subsequently, teriparatide was delivered by standard daily injection at 20 mcg doses and after explant of the device in 40 mcg doses. The primary outcomes were pharmacokinetic and pharmacodynamic, with serial blood sampling performed on 4 separate days after microchip teriparatide delivery, on 2 days after 20 mcg subcutaneous injections, and on 2 days after 40 mcg subcutaneous injections (2 standard 20 mcg doses delivered sequentially, second dose delivered within presumably seconds via the same pen/needle).

In one volunteer, the delivery system failed completely due to a 'faulty component in the membrane activation circuitry required to release the drug'. All results were excluded from this volunteer. Pharmacokinetics (PK) and pharmacodynamics results for the other seven women were presented. Safety profiles in this small study were similar to those seen with daily injectable teriparatide. Critical to the clinical efficacy of teriparatide is a tight PK profile required to produce an anabolic, rather than a catabolic effect. To this end, the microchip implantable delivery device appeared very successful. In fact, the pharmacokinetic profile of PTH delivered by indwelling microchip was even more consistent, with lower variability than subcutaneous injectable delivery. PK variables from implantable teriparatide were very similar compared with historical results obtained from 20 and 40 mcg teriparatide injections.[22] PK variables from implantable teriparatide were also compared with two 20 mcg teriparatide injections from this trial (no single 40 mcg injectable dose was available). From these latter analyses, the average maximal concentration of PTH (1–34) was almost identical to that seen with two 20-mcg teriparatide injections. However, the average time to maximum concentration was about double the time for teriparatide injections, and the terminal half-life for teriparatide delivered by the implantable device was about 30% longer. Whether this could translate into any difference in bioactivity is unknown. Serum calcium levels rose similarly within 6 h of either implantable or injectable teriparatide delivery. The expected biochemical increment in procollagen type-1 amino-terminal propeptide was also seen with implantable device delivery (peak increase 143%), with no change in c-telopeptide during this short-term trial (also as expected). However, because this pilot trial included implantable teriparatide and injectable teriparatide in the same patients, biochemical markers were measured sequentially over time. As biochemical responses to teriparatide follow distinct chronological sequences, there was no ability to compare the magnitude of the pharmacodynamic biochemical marker response to implantable versus injectable delivery. A comparison of biochemical marker responses to 20 mcg doses by implantable delivery versus 20 mcg by subcutaneous injection (the approved teriparatide dose) will be required in the future clinical development program.

Ultimately, what proportion of patients would find the implantable procedure preferable to daily injections is unknown (the device would require at least three to five procedures with implantation and explantation to be implanted two to four times over a 2-year treatment course, and explanted three to five times). Apparently, the women in the pilot study reported no adverse effects on quality of life and would be willing to have another implantable device.[20] However, some people will be concerned about the long-term effects of a foreign body implantation. Many patients experience minor adverse reactions to teriparatide, especially the first few weeks. Sometimes, creative dosing schedules, such as skipping days between medication doses, can help alleviate the early and transitory side effects associated with teriparatide and can help keep people on therapy until the side effects resolve. Although this small pilot study did not test this approach, the remote control of dose administration could be used to alter the dosing schedule similarly to day-to-day dosing changes that can be made with standard subcutaneous injections.

There is no doubt that the microchip delivery system is a major biotechnological advance in drug delivery. The data in this trial provide the proof of concept and suggest that further longer-term studies should be undertaken for patients who need daily injectable therapies for up to a year or more. Although the cost might be similar to the cost of standard daily teriparatide, the indwelling delivery might improve compliance and persistence in some groups of patients. Additional studies to monitor for rejection, infection and waning pharmacokinetic efficacy over longer time periods are required. Moreover, a failure rate for the device of over 10% of individuals is too high and needs to be improved for ultimate clinical utility. Of 140 doses expected in the other 7 women in this pilot study, 132 were delivered, although 16 of the 132 had only partial delivery of the medication. Full medication dose was therefore administered in 116 of the expected 140 (or of the expected 160, including the woman with device failure). Improvements in manufacturing to increase the proportion of full doses of drug delivered, and of course expansion in the number of possible doses deliverable (6–12 months of therapy within each implantable device) would be expected in the next phase of development.

Any delivery system that can help patients take advantage of an extremely valuable and unique therapy in the treatment of osteoporosis in patients at high risk of fracture represents a significant advance in the field.

Conflict of Interest

Dr Cosman has received honoraria for speaking, consulting and advising from Eli Lilly, Novartis and Amgen, and consulting and advising for Merck.

References

1. McClung MR, San Martin J, Miller PD, Civitelli R, Bandeira F, Omizo M *et al.* Opposite bone remodeling effects of teriparatide and alendronate in increasing bone mass. *Arch Intern Med* 2005;**165**:1762–1768.
2. Arlot M, Meunier PJ, Boivin G, Haddock L, Tamayo J, Correa-Rotter R *et al.* Differential effects of teriparatide and alendronate on bone remodeling in postmenopausal women assessed by histomorphometric parameters. *J Bone Miner Res* 2005;**20**:1244–1253.
3. Lindsay R, Cosman F, Zhou H, Bostrom MP, Shen VW, Cruz JD *et al.* A novel tetracycline labeling schedule for longitudinal evaluation of the short-term effects of anabolic therapy with a single iliac crest bone biopsy: early actions of teriparatide. *J Bone Miner Res* 2006;**21**: 366–373.
4. Dempster DW, Cosman F, Kurland ES, Zhou H, Nieves J, Woelfert L *et al.* Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: a paired biopsy study. *J Bone Miner Res* 2001;**16**:1846–1853.
5. Jiang Y, Zhao JJ, Mitlak BH, Wang O, Genant HK, Eriksen EF. Recombinant human parathyroid hormone (1-34) [teriparatide] improves both cortical and cancellous bone structure. *J Bone Miner Res* 2003;**18**:1932–1941.
6. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY *et al.* Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;**344**:1434–1441.
7. Marcus R, Wang O, Satterwhite J, Mitlak B. The skeletal response to teriparatide is largely independent of age, initial bone mineral density, and prevalent vertebral fractures in postmenopausal women with osteoporosis. *J Bone Miner Res* 2003;**18**:18–23.
8. Burr DB. Does early PTH treatment compromise bone strength? The balance between remodeling, porosity, bone mineral, and bone size. *Curr Osteoporos Rep* 2005;**3**:19–24.
9. Parfitt AM. Parathyroid hormone and periosteal bone expansion. *J Bone Miner Res* 2002; **17**:1741–1743.
10. Lindsay R, Zhou H, Cosman F, Nieves J, Dempster DW, Hodsman AB. Effects of a one-month treatment with PTH(1-34) on bone formation on cancellous, endocortical, and periosteal surfaces of the human ilium. *J Bone Miner Res* 2007;**22**:495–502.
11. Ma YL, Marin F, Stepan J, Ish-Shalom S, Möricke R, Hawkins F *et al.* Comparative effects of teriparatide and strontium ranelate in the periosteum of iliac crest biopsies in postmenopausal women with osteoporosis. *Bone* 2011;**48**:972–978.
12. Dempster DW, Zhou H, Recker RR, Brown JP, Bolognese MA, Recknor CP *et al.* Skeletal histomorphometry in subjects on teriparatide or zoledronic acid therapy (SHOTZ) study: a randomized controlled trial. *J Clin Endocrinol Metab* 2012;**97**:2799–2808.

13. Rehman Q, Lang TF, Arnaud CD, Modin GW, Lane NE. Daily treatment with parathyroid hormone is associated with an increase in vertebral cross-sectional area in postmenopausal women with glucocorticoid-induced osteoporosis. *Osteoporos Int* 2003;**14**:77–81.
14. Zanchetta JR, Bogado CE, Ferretti JL, Wang O, Wilson MG, Sato M *et al.* Effects of teriparatide [recombinant human parathyroid hormone (1-34)] on cortical bone in postmenopausal women with osteoporosis. *J Bone Miner Res* 2003;**18**:539–543.
15. Uusi-Rasi K, Semanick LM, Zanchetta JR, Bogado CE, Eriksen EF, Sato M *et al.* Effects of teriparatide [rhPTH (1-34)] treatment on structural geometry of the proximal femur in elderly osteoporotic women. *Bone* 2005;**36**:948–958.
16. Body JJ, Gaich GA, Scheele WH, Kulkarni PM, Miller PD, Peretz A *et al.* A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-34)] with alendronate in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 2002;**87**:4528–4535.
17. Saag KG, Shane E, Boonen S, Marin F, Donley DW, Taylor KA *et al.* Teriparatide or alendronate in glucocorticoid-induced osteoporosis. *N Engl J Med* 2007;**357**:2028–2039.
18. Hadji P, Zanchetta JR, Russo L, Recknor CP, Saag KG, McKiernan FE *et al.* The effect of teriparatide compared with risedronate on reduction of back pain in postmenopausal women with osteoporotic vertebral fractures. *Osteoporos Int* 2011;**23**:2141–2150.
19. Cosman F, Lane NE, Bolognese MA, Zanchetta JR, Garcia-Hernandez PA, Sees K *et al.* Effect of transdermal teriparatide administration on bone mineral density in postmenopausal women. *J Clin Endocrinol Metab* 2010;**95**:151–158.
20. Farra R, Sheppard Jr NF, McCabe L, Neer RM, Anderson JM, Santini Jr JT *et al.* First-in-human testing of a wirelessly controlled drug delivery microchip. *Sci Transl Med* 2012;**4**:122ra21.
21. Maloney JM, Uhland SA, Polito BF, Sheppard Jr NF, Pelta CM, Santini Jr JT. Electrothermally activated microchips for implantable drug delivery and biosensing. *J Control Release* 2005;**109**:244–255.
22. Ahn HY. *Clinical Pharmacology and Biopharmaceutics Review*, 2002. Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring: MD. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-318_Forteo_biopharmr.pdf.