Is there a role for combination therapy for osteoporosis?

Felicia Cosman

Received: 19 March 2013 / Accepted: 4 April 2013 / Published online: 26 April 2013
© Springer Science+Business Media New York 2013

There is no single agent currently available that represents a cure for osteoporosis. Various anabolic and antiresorptive therapies have been combined, following different protocols, to attempt to attain superior bone mass and strength compared to monotherapy. There is a great deal of misunderstanding about results of these trials. The small randomized, blinded study in men with osteoporosis in this issue of the journal [1], evaluating a previously untested combination of teriparatide and risedronate compared with either agent alone, might help encourage some reconsideration of combination therapy for treatment of osteoporosis.

In trying to interpret the many different combination therapy studies [2, 3], it is important to make some distinctions between the populations that have been studied: previously untreated individuals receiving two agents concomitantly and individuals on established antiresorptive therapy where the anabolic agent is combined with continued antiresorptive therapy. While there are some parallels between these two populations, differences in the magnitude of active bone surface, effects of acute antiresorptive agents on parathyroid dynamics, and perhaps unique acute effects of antiresorptive agents on osteoblast function might all play a role in producing distinct responses to combination therapy in previously treated vs treatment naïve individuals. A third population of individuals who have been on prior bisphosphonates in the recent or remote past has not been adequately studied.

Several lines of work suggested that in patients who had already been treated with an oral bisphosphonate such as alendronate, there might be different effects in those who

switched to teriparatide [4–6] vs those in whom teriparatide was added [7]. In general, hip BMD declines in the first 6–12 months when teriparatide is given alone to these pretreated patients, whereas bone density increases modestly in those on combination treatment. In the only study to directly compare the effects of switching to teriparatide vs combining teriparatide with ongoing alendronate (in women who had already received prior alendronate for an average of over 4 years), DXA BMD changes in both spine and hip were greater in those randomized to combination therapy than teriparatide alone [8]. Furthermore, volumetric BMD of the hip declined in those who switched to teriparatide and increased in those who received combination therapy [9]. Although strength of the hip did not actually decline in the teriparatide alone group, hip strength increased in the combination group [9]. These findings have very important implications for the clinical use of teriparatide in patients who have received prior antiresorptive therapy and are at high risk for hip and other skeletal sites that are rich in cortical bone. It may be that the withdrawal of the bisphosphonate actually facilitates an exaggerated bone resorption response to teriparatide [8] and offsets the expected positive bone balance, particularly in the cortical skeleton where there is little incorporated bisphosphonate.

Some of the findings in this pretreated population can be applied to those of combination therapy studies in the treatment naïve population. In several of these studies, there was no apparent difference at 12 months in the response of spine BMD measured by DXA to combination treatment versus PTH or teriparatide monotherapy [10, 11], whereas a greater increase in hip BMD was seen with combination treatment compared to teriparatide alone. Even a short-term study of teriparatide plus raloxifene was consistent with these findings [12]; there was no difference

F. Cosman (✉)
Helen Hayes Hospital, West Haverstraw, NY, USA
e-mail: cosmanf@helenhayeshosp.org

in spine BMD accrual between combination and teriparatide alone groups, whereas there was a greater increment in hip BMD with combination therapy versus teriparatide alone at 6 months. In the small but well-executed study in this issue of the journal [1], a greater increase in hip BMD was seen with combined teriparatide plus risedronate versus teriparatide monotherapy.

The results from investigations in treatment naïve and treatment experienced individuals are consistent with a recently published trial with unique design. Muschitz et al. [13] investigated women treated with teriparatide for 9 months and then randomized to remain on teriparatide alone or add alendronate or raloxifene plus ongoing teriparatide for an additional 9 months. The BMD gains at the end of the study were significantly greater in both spine and total hip in the teriparatide/alendronate combination group compared to teriparatide alone. Consistent with the bone density results, with alendronate addition at 9 months to ongoing teriparatide, both PINP and CTX declined, the latter more prominently.

In the Walker trial [1], there are some inconsistencies compared with prior data that deserve mention. There was no significant difference between the spine BMD response of the combination (+6.95 %) or teriparatide group (+5.68 %) compared with the risedronate group (+3.76 %). The lack of statistical significance here is likely due to the very small sample size (9 completers per group). It is also surprising that there was no increase in spine BMD in the teriparatide group between 12 and 18 months (in fact there was a suggestion of decline). Similarly, there was no increase in BMD of the hip or femoral neck between 12 and 18 months in the teriparatide group. The modest BMD increments in this male population are consistent with another teriparatide study in men [14] and might relate to gender-specific pharmacokinetics with teriparatide, with lower systemic exposure in men, perhaps based on body size and weight or other factors [15]. In contrast to the minimal or nonexistent effects of teriparatide alone between 12 and 18 months at all sites, in the combination group the BMD effects were quite prominent in spine and hip between 12 and 18 months; however, at 18 months, only at the total hip did the difference in BMD gain between the combination and teriparatide groups achieve significance.

The most unique finding in this combination study was that the biochemical marker levels for both the formation and resorption markers (PINP and CTX) increased above baseline for the entire duration of the trial. With the PTH plus Alendronate [10] and Teriparatide plus Zoledronic Acid [11] trials, in the combination group, biochemical markers were below baseline for all or most of the 1-year study duration. Perhaps the difference relates to risedronate's modest antiresorptive potency (at the dose utilized, compared to alendronate or zoledronic acid). In the study

by Deal et al. [12], where teriparatide was combined with raloxifene, another low potency antiresorptive agent, the PINP level also increased above baseline at all measured time points (1, 3, and 6 months) and the CTX level was above baseline at 3 and 6 months.

It is clearly time to re-evaluate the potential benefits of combination therapy, with a careful attention to effects on both spine and hip. In patients who have previously received bisphosphonate agents, there is no question that different results are achieved at the hip and perhaps other sites rich in cortical bone with combination vs individual therapy. The current study by Walker et al. adds to the growing literature that suggests that even in patients who have not been on bisphosphonate treatment previously, a superior hip BMD response might also be achieved with combination therapy (in this case, teriparatide plus risedronate). These differences might be clinically meaningful, particularly for patients at highest risk for hip fractures, including those who have had a recent hip fracture, multiple prevalent fractures, or extremely low hip BMD.

References

1. Walker, M.D., Cusano, N.E., Sliney, J., Jr., Romano, M., Zhang, C., McMahon, D.J., Bilezikian, J.P.: Combination therapy with risedronate and teriparatide in male osteoporosis. *Endocrine* (2012). doi:[10.1007/s12020-012-9819-4](https://doi.org/10.1007/s12020-012-9819-4)
2. J. Compston, The use of combination therapy in the treatment of postmenopausal osteoporosis. *Endocrine* **41**(1), 11–18 (2012). doi:[10.1007/s12020-011-9554-2](https://doi.org/10.1007/s12020-011-9554-2)
3. G. Mazziotti, J. Bilezikian, E. Canalis, D. Cocchi, A. Giustina, New understanding and treatments for osteoporosis. *Endocrine* **41**(1), 58–69 (2012). doi:[10.1007/s12020-011-9570-2](https://doi.org/10.1007/s12020-011-9570-2)
4. B. Ettinger, J. San Martin, G. Crans, I. Pavo, Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate. *J. Bone Miner. Res.* **19**(5), 745–751 (2004). doi:[10.1359/JBMR.040117](https://doi.org/10.1359/JBMR.040117)
5. P.D. Miller, P.D. Delmas, R. Lindsay, N.B. Watts, M. Luckey, J. Adachi, K. Saag, S.L. Greenspan, E. Seeman, S. Boonen, S. Meeves, T.F. Lang, J.P. Bilezikian, Early responsiveness of women with osteoporosis to teriparatide after therapy with alendronate or risedronate. *J. Clin. Endocrinol. Metab.* **93**(10), 3785–3793 (2008). doi:[10.1210/jc.2008-0353](https://doi.org/10.1210/jc.2008-0353)
6. S. Boonen, F. Marin, B. Obermayer-Pietsch, M.E. Simoes, C. Barker, E.V. Glass, P. Hadji, G. Lyritis, H. Oertel, T. Nickelsen, E.V. McCloskey, Effects of previous antiresorptive therapy on the bone mineral density response to two years of teriparatide treatment in postmenopausal women with osteoporosis. *J. Clin. Endocrinol. Metab.* **93**(3), 852–860 (2008)
7. F. Cosman, J. Nieves, M. Zion, L. Woelfert, M. Luckey, R. Lindsay, Daily and cyclic parathyroid hormone in women receiving alendronate. *N. Engl. J. Med.* **353**(6), 566–575 (2005)
8. F. Cosman, R.A. Wermers, C. Recknor, K.F. Mauck, L. Xie, E.V. Glass, J.H. Krege, 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.* **94**(10), 3772–3780 (2009). doi:[10.1210/jc.2008-2719](https://doi.org/10.1210/jc.2008-2719)

9. Cosman, F., Keaveny, T.M., Kopperdahl, D., Wermers, R.A., Wan, X., Krohn, K.D., Kregge, J.H.: Hip and spine strength effects of adding versus switching to teriparatide in postmenopausal women with osteoporosis treated with prior alendronate or raloxifene. *J. Bone Miner. Res.* n/a-n/a (2012). doi:[10.1002/jbmr.1853](https://doi.org/10.1002/jbmr.1853)
10. D.M. Black, S.L. Greenspan, K.E. Ensrud, L. Palermo, J.A. McGowan, T.F. Lang, P. Garnero, M.L. Bouxsein, J.P. Bilezikian, C.J. Rosen, T.H.S.I. Pa, The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *N. Eng. J. Med.* **349**(13), 1207–1215 (2003). doi:[10.1056/NEJMoa031975](https://doi.org/10.1056/NEJMoa031975)
11. F. Cosman, E.F. Eriksen, C. Recknor, P.D. Miller, N. Guanabens, C. Kasperk, P. Papanastasiou, A. Readie, H. Rao, J.A. Gasser, C. Bucci-Rechtweg, S. Boonen, Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1–34)] in postmenopausal osteoporosis. *J. Bone Miner. Res.* **26**(3), 503–511 (2011). doi:[10.1002/jbmr.238](https://doi.org/10.1002/jbmr.238)
12. C. Deal, M. Omizo, E.N. Schwartz, E.F. Eriksen, P. Cantor, J. Wang, E.V. Glass, S.L. Myers, J.H. Kregge, Combination teriparatide and raloxifene therapy for postmenopausal osteoporosis: results from a 6-month double-blind placebo-controlled trial. *J. Bone Miner. Res.* **20**(11), 1905–1911 (2005). doi:[10.1359/JBMR.050714](https://doi.org/10.1359/JBMR.050714)
13. C. Muschitz, R. Kocijan, A. Fahrleitner-Pammer, S. Lung, H. Resch, Antiresorptives overlapping ongoing teriparatide treatment result in additional increases in bone mineral density. *J. Bone Miner. Res.* **28**(1), 196–205 (2013). doi:[10.1002/jbmr.1716](https://doi.org/10.1002/jbmr.1716)
14. E.S. Orwoll, W.H. Scheele, S. Paul, S. Adami, U. Syversen, A. Diez-Perez, J.M. Kaufman, A.D. Clancy, G.A. Gaich, The effect of teriparatide [human parathyroid hormone (1–34)] therapy on bone density in men with osteoporosis. *J. Bone Miner. Res.* **18**(1), 9–17 (2003). doi:[10.1359/jbmr.2003.18.1.9](https://doi.org/10.1359/jbmr.2003.18.1.9)
15. R. Marcus, O. Wang, J. Satterwhite, B. Mitlak, 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.* **18**(1), 18–23 (2003). doi:[10.1359/jbmr.2003.18.1.18](https://doi.org/10.1359/jbmr.2003.18.1.18)