PERSPECTIVE

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Treatment Sequence Matters: Anabolic and Antiresorptive Therapy for Osteoporosis

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ABSTRACT

The effects of anabolic medications (teriparatide [TPTD] and parathyroid hormone [PTH]) differ in patients who have received recent treatment with potent antiresorptives. This perspective reviews studies evaluating bone density (BMD) and histomorphometric effects of treatment sequences beginning with TPTD/PTH followed by potent antiresorptives and those beginning with potent antiresorptives followed by switching to or adding TPTD. Effect of treatment sequence on spine BMD outcome is minor, with modest quantitative differences. However, when individuals established on potent bisphosphonates are switched to TPTD, hip BMD declines below baseline for at least the first 12 months after the switch to TPTD. This transient hip BMD loss is more prominent when the antiresorptive is denosumab; in this setting, hip BMD remains below baseline for almost a full 24 months. In a controlled comparison of those who switched from alendronate to TPTD versus those who added TPTD to ongoing alendronate, the effect on hip BMD was improved with combination therapy. Furthermore, hip strength improved with the addition of TPTD to ongoing alendronate, whereas it was neutral after switching from alendronate to TPTD, primarily due to the effect on cortical bone. Bone biopsy studies indicate that TPTD stimulates bone formation in patients who have not been treated previously as well as in patients on prior and ongoing bisphosphonates. Histomorphometric evidence suggests that use of alendronate with TPTD blocks the TPTD-induced increase in cortical porosity. When possible, we suggest anabolic therapy first, followed by potent antiresorptive therapy. The common practice of switching to TPTD only after patients have an inadequate response to antiresorptives (intercurrent fracture or inadequate BMD effect) is not the optimal utilization of anabolic treatment. In fact, this may result in transient loss of hip BMD and strength. In this setting, continuing a potent antiresorptive while starting TPTD might improve hip outcomes. © 2017 American Society for Bone and Mineral Research.

KEY WORDS: ANABOLIC; ANTIRESORPTIVE; TERIPARATIDE; TREATMENT SEQUENCE; BONE DENSITY

Introduction

The majority of osteoporosis medications are antiresorptive agents, which reduce the rate of bone remodeling. Within this group are the bisphosphonates, which inhibit protein prenylation in the mature osteoclast, reducing osteoclast capacity to resorb bone,[1] and denosumab, a monoclonal antibody to RANK ligand that inhibits osteoclast formation, function, and survival.[2] Although several new anabolic agents are in development,[3–5] teriparatide is currently the only available anabolic therapy for osteoporosis in the United States, with the addition of only PTH(1-84) in the EU (referred to as PTH). Teriparatide (TPTD) and PTH act by direct stimulation of osteoblast activity and recruitment (both remodeling and modeling-based formation) as well as stimulation of remodeling, favoring bone formation (remodeling-based formation). Both effects increase bone formation rate in cancellous, endocortical, and periosteal envelopes and augment the thickness of bone packets.[6–10] Both anabolic and potent antiresorptive agents (bisphosphonates, denosumab) improve bone mineral density (BMD) and reduce risk of fracture in patients who have not been on prior osteoporosis treatments.[11–17] Effects of most osteoporosis medications differ, however, in patients who have already been pretreated with other potent osteoporosis medications.[18–23] This is certainly true of TPTD and PTH.[24–30]

BMD responses to initial TPTD/PTH followed by potent antiresorptive therapy are substantial in both spine and hip sites as a result of the effects of both components of the treatment sequence.[28,31–34] In contrast, several studies have indicated that hip BMD responses to TPTD are lower in patients who have already been pretreated with potent antiresorptive therapies and consistently decline transiently for the first year or even longer.[24–28,30] Although there are no fracture endpoint trials in these antiresorptive pretreated patients, the substantial differences in BMD outcome, particularly for the hip region, suggest

Received in original form October 27, 2016; revised form November 29, 2016; accepted December 1, 2016. Accepted manuscript online December 1, 2016.
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Journal of Bone and Mineral Research, Vol. 32, No. 2, February 2017, pp 198–202
DOI: 10.1002/jbmr.3051

that TPTD effects against fracture could also differ in these pretreated patients. More than 50% of TPTD prescriptions are written for this group of patients,[35] so these observations have important clinical significance.

This perspective reviews studies evaluating BMD and histomorphometric effects of treatment sequences beginning with TPTD or PTH followed by potent antiresorptive agents and those beginning with potent antiresorptive agents followed by switching to or adding TPTD. We concentrate on the hip region because the effects of treatment sequence at that site are more dramatic than those found for the spine. In the spine, effects of TPTD after bisphosphonates and denosumab remain positive, although slightly blunted.[24–28,30–34] Furthermore, even after transition from denosumab to TPTD, the resultant spine BMD level was the same 2 years after the transition as it was when the sequence began with TPTD followed by denosumab.[28] The findings are very different for the hip region, as we describe below. Our perspective will focus on the effects of treatment sequence when the more potent antiresorptive agents (bisphosphonates and denosumab) are used. Changes in both hip and spine BMD are much less affected by treatment sequence when the prior antiresorptive agent is hormone therapy or raloxifene.[25–27,36–38] Furthermore, these agents are not in general appropriate for treatment of more severe osteoporosis.

Effects of Sequential Treatment on Hip BMD

In treatment-naive women, PTH for 1 year increases total hip (TH) and femoral neck (FN) BMD by 0% to 1%, and after transition to alendronate for an additional year, BMD increases by an additional 3% to 4%.[31,33] TPTD in treatment-naive postmenopausal women over 19 to 24 months increases hip BMD more than PTH, resulting in an average gain of about 3% in the TH and FN.[15,28,29,39] After TPTD, transition to a bisphosphonate leads to further increases of about 2% in both the TH and FN after 1 year.[32] After transition from TPTD to sequential denosumab, BMD increments in the TH and FN are even higher (about 6% in both sites after 1 year of denosumab).[28]

In contrast, Table 1 lists the hip BMD results when individuals established on potent antiresorptive therapies are switched to TPTD. Data are presented for change at 6, 12, 18, and 24 months where available. The average effects over each available time point indicate that BMD changes in the hip are below baseline for the first 12 months after a switch to TPTD, unchanged from baseline at 18 months and slightly above baseline at 24 months.[24,26–28,30] The findings differ somewhat after switching from bisphosphonates compared with switching from denosumab to TPTD; at 18 months, hip BMD is slightly above baseline after switching from bisphosphonates but still below baseline after switching from denosumab. Furthermore, after 24 months of TPTD, hip BMD is increased by 2% to 3% after a switch from bisphosphonates but still below baseline after a switch from denosumab. The differences in BMD response to switching from alendronate versus denosumab to TPTD are consistent with differences in the bone turnover marker responses to switching from these different antiresorptive agents. Marker levels (of both bone resorption and formation) increase substantially over 6 to 12 months after switching from either alendronate or denosumab to TPTD; however, the marker level increases are far more dramatic after switching from denosumab to TPTD. At 6 months, C-terminal telopeptide (CTX) levels increase from the on-alendronate baseline by approximately two- to threefold,[26] whereas the CTX levels increase from the on-denosumab baseline by more than ninefold.[28] Furthermore, the median CTX level attained after switching from denosumab is more than double the median level acheived after switching from alendronate.

The impact on BMD of a 48-month treatment sequence was studied formally by Leder and colleagues.[28] This study allows direct comparison of a 4-year sequence of TPTD for 2 years, followed by denosumab for 2 years, compared with the opposite sequence, denosumab for 2 years followed by TPTD for 2 years. Over 4 years, in the group that transitioned from TPTD to denosumab, mean TH and FN BMD increased 6.6% and 8.3%, respectively. In contrast, in those who switched from denosumab to TPTD, BMD at the TH and FN declined precipitously for the entire first year and levels were still below the end-of-denosumab treatment baseline for the TH and just above that baseline for the FN. The entire 48-month sequence when denosumab is administered first, followed by TPTD, resulted in mean TH and FN increments of 2.8% and 4.9% (approximately 50% lower hip BMD gains compared with the sequence of TPTD followed by denosumab, all significantly different versus the former sequence). Furthermore, after transition from 24 months of denosumab to 24 months of TPTD, progressive bone loss at the radius was also found, in contrast to a slight increase in radius BMD when TPTD was given followed by denosumab.[28]

Comparison of Switching From Antiresorptive to TPTD Versus Adding Antiresorptive to TPTD

A formal randomized trial compared the effect of continuing versus stopping the antiresorptive agent when TPTD was initiated in 102 women on prior alendronate and 96 on prior raloxifene.[26] Women within each antiresorptive cohort were

Table 1. Hip BMD Effect of Switching From Potent Antiresorptive Therapy to TPTD

			% Change in total hip BMD during TPTD/PTH treatment			
Study	Sample size	Treatment paradigm	6 mo	12 mo	18 mo	24 mo
Ettinger et al.[27]	33	Alendronate (mean 29.3 mo) → TPTD (18 mo)	–1.8%	–1.0%	+0.3%	–
Boonen et al.[24]	107	Alendronate (median 29.2 mo) → TPTD (24 mo)	–1.2%	–0.6%	+0.6%	+2.1%
Boonen et al.[24]	59	Risedronate (median 23.4 mo) → TPTD (24 mo)	–1.6%	–0.4%	+0.9%	+2.9%
Miller et al.[30]	158	Risedronate (mean 37.2 mo) → TPTD (12 mo)	–1.2%	–0.3%	–	–
Miller et al.[30]	166	Alendronate (mean 38.0 mo) → TPTD (12 mo)	–1.9%	–1.7%	–	–
Cosman et al.[26]	50	Alendronate (mean 45.7 mo) → TPTD (18 mo)	–0.8%	–	+0.9%	–
Leder et al.[28]	27	Denosumab (24 mo) → TPTD (24 mo)	–1.7%	–2.7%	–1.7%	–0.7%

mo = months.

In some cases, numbers are estimated by extrapolation from graph in article.

randomized to switch to or to add TPTD. Differences between combination and switch protocols were minor with raloxifene pretreatment. However, in the group that switched from alendronate to TPTD, there was an increase in the biochemical resorption marker, serum CTX, within 1 month (similar to that found in a prior study where women transitioned from alendronate or risedronate to TPTD).[30] In general, serum CTX levels do not increase within 1 month of TPTD initiation in previously untreated individuals, so this appears to represent a more pronounced early stimulation of bone remodeling. TH BMD declined in the first 6 months after TPTD administration (as found in switch studies described above and in Table 1).[24,26–28,30] BMD increases at both 6 and 18 months at both spine and TH were greater in those patients who added TPTD to ongoing alendronate compared with those who switched to TPTD. At no time point did TH BMD decline with combination treatment, and after 18 months, in the TPTD plus alendronate group, TH BMD increased 3.2% compared with 0.9% in the group that switched from alendronate to TPTD ($p < 0.05$ group difference). Moreover, quantitative computed tomography (QCT) measurements of the hip further support the findings from areal BMD outcomes. Volumetric TH BMD of the integral bone (including cancellous and peripheral cortical bone) increased significantly in the group that added TPTD to ongoing alendronate but did not change in the group that switched to TPTD (group difference $p = 0.002$).[24] Utilizing finite element models to estimate bone strength from QCT scans in this study, hip strength did not increase after 18 months of TPTD in patients who switched from alendronate to TPTD, whereas hip strength did increase in patients who added TPTD to ongoing alendronate.[25] Separation of QCT measurements into trabecular and cortical (peripheral) compartments indicated that cortical volumetric BMD declined (perhaps as a result of increasing cortical porosity), in those who switched from alendronate to TPTD, but increased in those who added TPTD to ongoing alendronate. In those who switched from alendronate to TPTD, the effect on hip strength of the cortical compartment was neutral; however, hip strength of the cortical compartment increased in those who added TPTD.

Effects of Sequential Treatment at the Tissue Level

Cancellous envelope

Few studies have assessed the effects of sequential treatment on iliac crest histomorphometry. Stepan and colleagues[40] analyzed paired biopsies taken at baseline and after 24 months of TPTD treatment from alendronate-pretreated and treatment-naive subjects. Remodeling activation frequency in cancellous bone increased by comparable amounts in both groups when compared with baseline. Recently, Fahrleitner-Pammer and colleagues[41] have reported improvement in cancellous bone volume in these same two groups of patients, although a nominally superior response was found in the treatment-naive group. These studies suggest that TPTD is effective at stimulating cancellous bone formation and improving mass and structure in treatment-naive and alendronate-pretreated individuals.

Cortical bone envelope

Using the biopsy samples from the same study, Ma and colleagues[42] focused on the histomorphometry of cortical bone. At baseline, dynamic parameters of bone formation on the periosteal, endocortical, and intracortical surfaces were generally lower in the alendronate-pretreated than in the treatment-naive group (as expected). After TPTD, these parameters increased in both groups, but at the end of the treatment period, most bone formation indices were higher in the treatment-naive group than in the alendronate-pretreated group. TPTD treatment increased endocortical wall width in both treatment groups and significantly increased cortical thickness. However, it also increased cortical porosity in the alendronate-pretreated group *switched* to TPTD. In a recent study,[10] our group compared the short-term bone-formation response to TPTD in treatment-naive subjects and in subjects on prior and ongoing alendronate. Biopsies taken at 7 weeks and at 7 months revealed that both treatment-naive and alendronate-treated groups responded to TPTD with an increase in bone formation, although the response was quantitatively lower in the alendronate-treated group. However, at 7 months of TPTD treatment, cortical porosity was higher in the treatment-naive than in the alendronate-treated group (in whom TPTD was *added* to ongoing alendronate).

Taken together, the histomorphometric data suggest that TPTD can stimulate bone formation and increase cancellous bone volume in alendronate-pretreated subjects, even in subjects in whom TPTD is added to ongoing alendronate treatment. Adding TPTD to ongoing alendronate treatment may prevent the increase in cortical porosity observed in individuals switched from alendronate to TPTD. As far as we know, there have been no histomorphometric studies where the effect of switching from alendronate (or any other potent antiresorptive agent) to TPTD has been compared with the effect of adding TPTD to ongoing alendronate. There are also no clinical bone biopsy data on the effects of following a course of TPTD/PTH with a potent antiresorptive agent.

It is important to note that the effects of a transient increase in cortical porosity by switching to TPTD could, in the long run, be offset by increased endocortical and intracortical bone formation.[43] Furthermore, the implications of new bone and osteocyte regeneration by TPTD/PTH, albeit with temporary loss of cortical mass and increased cortical porosity, might ultimately enhance skeletal strength. However, it is also possible that the acute effects on cortical porosity could be detrimental, particularly for patients at imminent risk of a cortical fracture (for example, recent hip fracture patients). It is also possible that continued antiresorptive administration will limit the TPTD/PTH-induced increase in volume of bone resorbed within each remodeling unit and facilitate a positive balance of formation to resorption with combination therapy.[44]

The most likely mechanisms for the major difference in hip BMD response when a potent antiresorptive agent is followed by TPTD/PTH (compared with the opposite sequence) is excessive bone remodeling with loss of denosumab- and bisphosphonate-induced inhibition of osteoclastic activity, combined with stimulation of remodeling by TPTD/PTH. In the setting of prior bisphosphonate treatment, this may be most apparent in the cortical skeleton where there is little buried bisphosphonate. In the setting of prior denosumab treatment, it may simply be that bone resorption occurs so rapidly in the cortical compartment that bone formation cannot keep up, leading to a precipitous decline in hip BMD. Although bone resorption also increases rapidly in cancellous bone after transition from denosumab to TPTD, the TPTD-induced increase in bone formation is also more rapid in the spine, leading to only a very minor transient loss that is quickly reversed.[28] The resultant BMD achieved after 2 years

with transition from denosumab spine to TPTD is indistinguishable from the spine BMD level achieved when TPTD is given first, followed by denosumab. The situation is slightly different in individuals after transition from alendronate to TPTD where spine BMD does not increase as dramatically as in women who transition from TPTD to alendronate.[24–33] However, this effect is minor compared with the effect of treatment sequence on BMD changes at the hip.

Alternative explanations for the decline in BMD when switching from a potent antiresorptive agent to TPTD include replacement of older highly mineralized bone with bone of low mineralization density, which will ultimately mineralize and restore BMD, as suggested by Eriksen and Brown.[45] However, even if the BMD decline is only temporary, it may offset other positive effects of anabolic therapy on bone strength during that time period. Whitmarsh and colleagues showed increased cortical thickness in patients who switched from alendronate to TPTD but reduced cortical BMD and cortical mass surface density compared with patients who added TPTD to ongoing alendronate.[46] Which of these parameters is most reflective of bone strength is unknown; however, finite element modeling of the femur in patients who switched to TPTD versus those in whom TPTD was added suggested that strength increased in the *add*, but not *switch*, setting. Theoretical advantages of the sequence of bisphosphonates or denosumab followed by TPTD must be weighed against the consistent (temporary) decline in hip BMD, increase in cortical porosity, and lack of increase in hip strength compared with the effects of *adding* TPTD to continuing antiresorptive treatment. With this latter approach, it is likely that a greater proportion of the TPTD-induced bone formation is modeling based, rather than remodeling based. There are no direct data to indicate whether there is an advantage of one versus the other mechanism for stimulation of bone formation. With the de novo combination of TPTD and denosumab, most of the TPTD-induced bone formation is likely to be modeling based because denosumab is such a potent resorption inhibitor, even when combined with TPTD.[47,48] With the de novo combination treatment, both spine and hip BMD increments were larger than observed with either agent alone, and high-resolution peripheral QCT indicated that the TPTD-induced increment in cortical porosity was reduced in the radius and tibia with combination therapy.[49]

Conclusion

In cases where patients are treatment naive, we suggest initiation of anabolic therapy first, followed by potent antiresorptive therapy whenever possible. In the setting of first-line therapy with TPTD, anti-fracture efficacy throughout the skeleton is conclusive, including sites with predominantly cortical bone, and evidence suggests that TPTD stimulates bone formation rapidly in the femoral neck.[50] However, our observations clearly highlight that the common practice of providing patients with first-line antiresorptive therapy and then only after patients have an inadequate BMD response and/or an intercurrent fracture to switch to TPTD is not the optimal utilization of anabolic treatment. An extremely important clinical issue is the patient who is currently being treated with a bisphosphonate or denosumab who sustains a hip fracture. The transition to TPTD might in fact lead to a transient loss of strength in cortical sites, including the other hip. This is critically important in patients with a recent fracture where we know the risk of a second imminent fracture is extremely high (~10% in the following year).[51,52] In cases such as these, we suggest consideration of combination treatment with utilization of potent antiresorptive therapy and addition of TPTD, for up to 2 years, to improve skeletal strength during this critical period.

Disclosures

FC and DWD: Advisor, Speaker, and Grant Recipient from Amgen and Eli Lilly, Advisor for Radius and Merck and consultant for Tarsa. JWN no disclosures.

References

1. Russell RGG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. Osteoporos Int. 2008;19 (6):733–59.
2. Lacey DL, Boyle WJ, Simonet WS, et al. Bench to bedside: elucidation of the OPG-RANK-RANKL pathway and the development of denosumab. Nat Rev Drug Discov. 2012;11(5):401–19.
3. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med. 2016; 375(16):1532–43.
4. Miller PD, Hattersley G, Riis BJ, et al. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. JAMA. 2016;316(7):722–33.
5. Cosman F, Hattersley G, Hu MY, Williams GC, Fitzpatrick LA, Black DM. Effects of abaloparatide-SC on fractures and bone mineral density in subgroups of postmenopausal women with osteoporosis and varying baseline risk factors. J Bone Miner Res. Epub 2016 Sep 9. DOI: 10.1002/jbmr.2991.
6. 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(11):1932–41.
7. Dempster DW, Zhou H, Recker RR, et al. Skeletal histomorphometry in subjects on teriparatide or zoledronic acid therapy (SHOTZ) study: a randomized controlled trial. J Clin Endocrinol Metab. 2012;97 (8):2799–808.
8. Lindsay R, Cosman F, Zhou H, 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(3):366–73.
9. 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(4):495–502.
10. Dempster DW, Cosman F, Zhou H, Nieves JW, Bostrom M, Lindsay R. Effects of daily or cyclic teriparatide on bone formation in the iliac crest in women on no prior therapy and in women on alendronate. J Bone Miner Res. 2016;31(8):1518–26.
11. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet. 1996; 348(9041):1535–41.
12. Lyles KW, Colon-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med. 2007;357(18):1799–809.
13. Chesnut IC, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res. 2004;19(8):1241–9.
14. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361(8):756–65.
15. Neer RM, Arnaud CD, Zanchetta JR, 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(19):1434–41.

16. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA. 1999; 282 (14):1344–52.
17. Greenspan SL, Bone HG, Ettinger MP, et al. Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. Ann Intern Med. 2007;146(5):326–39.
18. Eiken P, Vestergaard P. Treatment of osteoporosis after alendronate or risedronate. Osteoporos Int. 2016;27(1):1–12.
19. McClung M, Recker R, Miller P, et al. Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. Bone. 2007;41(1): 122–8.
20. Kendler DL, Roux C, Benhamou CL, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. J Bone Miner Res. 2010; 25(1):72–81.
21. Freemantle N, Satram-Hoang S, Tang ET, et al. Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. Osteoporos Int. 2012;23(1):317–26.
22. Roux C, Hofbauer LC, Ho PR, et al. Denosumab compared with risedronate in postmenopausal women suboptimally adherent to alendronate therapy: efficacy and safety results from a randomized open-label study. Bone. 2014;58:48–54.
23. Recknor C, Czerwinski E, Bone HG, et al. Denosumab compared with ibandronate in postmenopausal women previously treated with bisphosphonate therapy: a randomized open-label trial. Obstet Gynecol. 2013;121(6):1291–9.
24. Boonen S, Marin F, Obermayer-Pietsch B, et al. 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. 2008;93(3):852–60.
25. Cosman F, Keaveny TM, Kopperdahl D, et al. 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. 2013;28(6):1328–36.
26. Cosman F, Wermers RA, Recknor C, et al. 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;94(10): 3772–80.
27. Ettinger B, San Martin J, Crans G, Pavo I. Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate. J Bone Miner Res. 2004;19(5):745–51.
28. Leder BZ, Tsai JN, Uihlein AV, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. Lancet. 2015; 386(9999):1147–55.
29. Cosman F, Nieves JW, Zion M, et al. Daily or cyclical teriparatide treatment in women with osteoporosis on no prior therapy and women on alendronate. J Clin Endocrinol Metab. 2015;100(7):2769–76.
30. Miller PD, Delmas PD, Lindsay R, et al. Early responsiveness of women with osteoporosis to teriparatide after therapy with alendronate or risedronate. J Clin Endocrinol Metab. 2008;93(10):3785–93.
31. Rittmaster RS, Bolognese M, Ettinger MP, et al. Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate. J Clin Endocrinol Metab. 2000;85(6):2129–34.
32. Prince R, Sipos A, Hossain A, et al. Sustained nonvertebral fragility fracture risk reduction after discontinuation of teriparatide treatment. J Bone Miner Res. 2005;20(9):1507–13.
33. Black DM, Bilezikian JP, Ensrud KE, et al. One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis. N Engl J Med. 2005;353(6):555–65.
34. Lindsay R, Scheele WH, Neer R, et al. Sustained vertebral fracture risk reduction after withdrawal of teriparatide in postmenopausal women with osteoporosis. Arch Intern Med. 2004;164(18):2024–30.
35. Bonafede MM, Shi N, Bower AG, Barron RL, Grauer A, Chandler DB. Teriparatide treatment patterns in osteoporosis and subsequent fracture events: a US claims analysis. Osteoporos Int. 2015;26(3): 1203–12.
36. Cosman F, Nieves JW, Zion M, Barbuto N, Lindsay R. Effect of prior and ongoing raloxifene therapy on response to PTH and maintenance of BMD after PTH therapy. Osteoporos Int. 2008;19(4):529–35.
37. Cosman F, Nieves J, Woelfert L, et al. Parathyroid hormone added to established hormone therapy: effects on vertebral fracture and maintenance of bone mass after parathyroid hormone withdrawal. J Bone Miner Res. 2001;16(5):925–31.
38. Eastell R, Nickelsen T, Marin F, et al. Sequential treatment of severe postmenopausal osteoporosis after teriparatide: final results of the randomized, controlled European Study of Forsteo (EUROFORS). J Bone Miner Res. 2009;24(4):726–36.
39. Obermayer-Pietsch BM, Marin F, McCloskey EV, et al. Effects of two years of daily teriparatide treatment on BMD in postmenopausal women with severe osteoporosis with and without prior antiresorptive treatment. J Bone Miner Res. 2008;23(10):1591–600.
40. Stepan JJ, Burr DB, Li J, et al. Histomorphometric changes by teriparatide in alendronate-pretreated women with osteoporosis. Osteoporos Int. 2010;21(12):2027–36.
41. Fahrleitner-Pammer A, Burr D, Dobnig H, et al. Improvement of cancellous bone microstructure in patients on teriparatide following alendronate pretreatment. Bone. 2016;89:16–24.
42. Ma YL, Zeng QQ, Chiang AY, et al. Effects of teriparatide on cortical histomorphometric variables in postmenopausal women with or without prior alendronate treatment. Bone. 2014;59:139–47.
43. Dempster DW, Zhou H, Recker RR, et al. A longitudinal study of skeletal histomorphometry at 6 and 24 months across four bone envelopes in postmenopausal women with osteoporosis receiving teriparatide or zoledronic acid in the SHOTZ trial. J Bone Miner Res. 2016;31(7):1429–39.
44. Seeman E, Martin TJ. Co-administration of antiresorptive and anabolic agents: a missed opportunity. J Bone Miner Res. 2015;30 (5):753–64.
45. Eriksen EF, Brown JP. Commentary: concurrent administration of PTH and antiresorptives: additive effects or DXA cosmetics. Bone. 2016;86:139–42.
46. Whitmarsh T, Treece GM, Gee AH, Poole KE. Mapping bone changes at the proximal femoral cortex of postmenopausal women in response to alendronate and teriparatide alone, combined or sequentially. J Bone Miner Res. 2015;30(7):1309–18.
47. Tsai JN, Uihlein AV, Lee H, et al. Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. Lancet. 2013;382(9886):50–6.
48. Leder BZ, Tsai JN, Uihlein AV, et al. Two years of denosumab and teriparatide administration in postmenopausal women with osteoporosis (The DATA Extension Study): a randomized controlled trial. J Clin Endocrinol Metab. 2014;99(5):1694–700.
49. Tsai JN, Uihlein AV, Burnett-Bowie SM, et al. Effects of two years of teriparatide, denosumab, or both on bone microarchitecture and strength (DATA-HRpQCT study). J Clin Endocrinol Metab. 2016;101 (5):2023–30.
50. Cosman F, Dempster DW, Nieves JW, et al. Effect of teriparatide on bone formation in the human femoral neck. J Clin Endocrinol Metab. 2016;101(4):1498–505.
51. Balasubramanian A, Zhang J, Chen L, et al. High risk of second fracture within 1, 2, 5 years after prior fracture among women 65 years or older. Presented at: ASBMR Annual Meeting; September 16–19, 2016; Atlanta, GA.
52. Colon-Emeric C, Kuchibhatla M, Pieper C, et al. The contribution of hip fracture to risk of subsequent fractures: data from two longitudinal studies. Osteoporos Int. 2003;14(11):879–83.