18

Combination and Sequential Osteoanabolic/Antiresorptive Therapy in Osteoporosis Treatment

Benjamin Z. Leder

Key Points

- The combination of teriparatide or other PTH-analogs and oral or intravenous bisphosphonates have not shown significant benefits compared to monotherapy.
- Conversely, the combination of teriparatide and denosumab increases bone density, improves skeletal microarchitecture, and augments estimated bone strength more than either of the drug alone.
- The mechanism underlying the efficacy of the denosumab/teriparatide combinations appears to be related to the capacity of denosumab to fully inhibit teriparatide-induced bone resorption while not interfering with teriparatide-induced modeling-based bone formation.
- The use of antiresorptive agents after osteoanabolic therapy is associated with continued anti-fracture efficacy, further increases in bone mass, and improvements in skeletal microarchitecture.
- Increases in bone mineral density are blunted when osteoanabolic therapy is used after bisphosphonate therapy.
- Patients who directly transition from denosumab-to-teriparatide experience rapid and significant high-turnover bone loss, and thus this particular sequential approach should be avoided.

Introduction

In contrast to many chronic conditions, such as hypertension or type 2 diabetes, that often require more than one drug to achieve clinical goals, the standard of osteoporosis care has historically involved the use of a single drug at a single dose. And despite the fact that several new antiresorptive and osteoanabolic agents have been introduced over the past decade, it remains the case that no single agent can cure osteoporosis. Thus, the need for more effective therapeutic regimens remains pressing, especially for those at the highest risk of fragility fracture.

An additional challenge to managing patients with established osteoporosis is an increasing reluctance to treat patients with antiresorptive medications for more than 3–5 years due to the concern over uncommon but serious side effects such as atypical femur fracture and osteonecrosis

B. Z. Leder (✉)
Endocrine Unit and Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
e-mail: bzleder@mgh.harvard.edu

B. Z. Leder, M. N. Wein (eds.), *Osteoporosis*, Contemporary Endocrinology,
https://doi.org/10.1007/978-3-319-69287-6_18

of the jaw, as well as the long-standing regulatory 2-year limit on parathyroid hormone receptor targeted osteoanabolic therapies [1–3]. Thus, it is expected that over a lifetime, the use of more than one medication will be required for many patients with established disease. In this setting, investigators have focused on evaluating the efficacy of combining antiresorptive and osteoanabolic drugs, an approach that was hypothesized to benefit from contrasting the drugs' differing mechanisms of action, as well using these medications in specific sequences. This chapter evaluates the available evidence concerning the differential effects of the various sequential and combination osteoporosis treatment strategies and details some of the important pharmacological and clinical distinctions between the various approaches.

Mechanisms of Current Osteoporosis Medications

Osteoanabolic Drugs

Currently, there are two available osteoporosis medications that can be classified as "anabolic" based on their capacity to increase osteoblastic bone formation. They are *teriparatide*, a parathyroid hormone (PTH) analog comprising the first 34 amino acids of the endogenous hormone and *abaloparatide*, a 34-amino-acid peptide that shares significant homology to parathyroid hormone-related protein (PTHrP). Both of these drugs target the same receptor. The anabolic potential of both teriparatide and ababloparatide appears to be dependent on intermittent administration as sustained receptor activation favors bone resorption over formation [4, 5].

One of the key unresolved questions concerning the mechanisms of these agents is what portion of their osteoanabolic effects are mediated through the initial stimulation of bone resorption: via the release of preformed growth factors from the bone matrix or via communication from osteoclasts to osteoblasts [6] versus direct stimulatory effects on osteoblasts, osteocytes, and bone lining cells [6, 7]. This question has direct relevance to the efficacy of combination therapy regimens, in that if resorption-dependent mechanisms were dominant, one would expect that combination strategies that more fully block bone resorption would be ineffective whereas if direct stimulatory effects on osteoblasts, osteocytes, or lining cells were dominant, combination strategies that more fully block bone resorption would be more effective than those that do so only partially. It has also been recently suggested that the subtle distinction in the pharmacological effects of PTH analogs may be based on their relative binding affinities to different PTH/PTHrP receptor conformations. Specifically, preclinical studies have suggested that PTH/PTHrP analogs distinguish between the two distinct receptor conformations (R^o and RG) and that more efficient binding to R^o leads to sustained signaling whereas more efficient binding to RG results in more transient signaling [8, 9]. It is thus conceivable that different signaling outputs triggered by the differential binding affinities of abaloparatide and teriparatide to the RG conformation, for example, may account for some of the observed differences in bone resorption rates and the incidence of hypercalcemia between these two agents [10]. Irrespective of mechanisms, however, it is well established that net skeletal effects of the currently approved PTH and PTHrP analogs are to increase trabecular bone mass and improve trabecular microarchitecture while concomitantly increasing cortical bone porosity [11–14]. It is also established that the subsequent clinical consequences of these skeletal changes are, in turn, an increase in bone strength and a clinically significant reduction in the risk of vertebral and nonvertebral fragility fractures in osteoporotic patients [15–22].

Antiresorptive Drugs

Antiresorptive medications act by inhibiting osteoclastic resorption of previously formed bone. The most commonly used antiresorptive medications are nitrogen-containing bisphosphonates that act by binding to hydroxyapatite and inhibiting the enzyme farnesyl diphosphate synthase in the cholesterol biosynthetic pathway,

suppressing protein geranylgeranylation, and hence osteoclastic bone resorption [23]. The various oral and intravenous bisphosphonates bind to hydroxyapatite with distinct affinities, and while they persist in bone for prolonged periods, there are differences in the endurance of their pharmacological effects (zoledronic acid > alendronate > ibandronate > risedronate) and these differences may account for their different pharmacological properties when combined with anabolic agents (as discussed in detail below) [24]. Denosumab is a monoclonal antibody that inhibits the binding of receptor activator of NFκB (RANK)-ligand to its osteoclast-derived receptor, RANK, thus inhibiting osteoclast formation, activation, and survival [25, 26]. Denosumab is the most rapidly acting and potent antiresorptive drug currently available but, unlike bisphosphonates, its effects are immediately reversible and rates of bone resorption and formation "rebound" to levels above the patient's original baseline levels when it is discontinued [27–32]. Estrogens and selective estrogen-receptor modulators exert their skeletal effects through binding to the estrogen receptor (ER)-α, playing a key role in both osteoblast and osteoclast biology. In the pharmacologic setting, however, these agents act primarily as antiresorptive drugs by suppressing stromal cell, osteoblast, and lining cell production of RANKL, increasing osteoblastic production of osteoprotegerin, directly suppressing the production of pro-resorptive cytokines, and promoting osteoclast apoptosis [33, 34]. Like denosumab, the antiresorptive effects of estrogens and selective estrogen-receptor modulators are immediately reversible, though a rebound phenomenon is not observed [35–37].

Combination Antiresorptive and Osteoanabolic Treatment

While the combination of multiple antiresorptive drugs has been studied in previous decades, these trials generally did not show a clinical benefit, and the introduction of more potent antiresorptives such as zoledronic acid and denosumab further dampened enthusiasm for this approach, leading to a focus on combining drugs of different mechanistic classes [38–46].

Combination of Estrogen or Selective Estrogen-Receptor Modulators and PTH Analogs

Some of the early studies assessing the efficacy of PTH analogs was performed in patients receiving ongoing estrogen administration but the lack of monotherapy comparator groups makes it is difficult to assess the relative benefits of these combinations versus the PTH analog alone [47–49]. In a 6-month double-blind, placebo-controlled trial study of 137 postmenopausal women randomized to receive teriparatide 20 μg daily either alone or combined with raloxifene 60 mg daily, combination therapy was shown to increase total hip BMD more than teriparatide monotherapy, though in this case the lack of a raloxifene monotherapy control group also limits clinical conclusions [50]. Thus, at present there is no conclusive evidence that combining PTH analogs with estrogens or selective estrogen-receptor modulators offers a clinical advantage.

Combination of Bisphosphonates and PTH Analogs

Most of the studies investigating combination osteoanabolic/antiresorptive treatment regimens have involved either teriparatide or PTH-(1-84) combined with the nitrogen-containing bisphosphonates. The first combination studies were performed utilizing the oral bisphosphonate, alendronate, and include the Parathyroid Hormone and Alendronate (PATH) study wherein 238 postmenopausal women with osteoporosis were randomized to receive PTH-(1-84) 100 μg daily, alendronate 10 mg daily, or both for 12 months [51]. As shown in the Table 18.1, 12-month increases in DXA-derived spine areal BMD were similar in all three treatment groups. However, at the total hip, combination therapy increased BMD more than the PTH-(1-84) alone but similarly to alendronate (of note, hip BMD

gains with PTH analogs in the first year of therapy are known to be absent or modest with subsequent larger gains if therapy is continued for 2 years) [54]. Additionally, PTH-(1-84) increased spine trabecular volumetric BMD (assessed by quantitative computed tomography or QCT) approximately twofold more than the combination of both medications. An assessment of biochemical markers of bone turnover in this study demonstrated that combination treatment suppressed bone resorption (serum c-telopeptide or CTX) less than alendronate monotherapy and that bone formation (type I collagen propeptide or P1NP) increased only transiently.

Two similar studies of combined teriparatide and alendronate were performed in postmenopausal osteoporotic women and osteoporotic men. In these studies, subjects were randomized to receive either alendronate 10 mg daily, teriparatide 40 μg daily, or both medications for 30 months, though teriparatide was not started until month 6 [55, 56]. In both of these populations, DXA-derived lumbar spine and femoral neck areal BMD increased more than two-fold more in those treated with teriparatide alone than those treated with alendronate alone or both medications. In another clinical trial utilizing PTH-(1-84), postmenopausal osteoporotic women were randomized to either 6 months of combined PTH-(1-84) and ibandronate 150 mg monthly followed by 18 months of ibandronate alone or two sequential courses of 3 months of PTH followed by 9 months of ibandronate alone and areal BMD of the spine and hip increased similarly in both groups [57].

The combination of teriparatide and the intravenous bisphosphonate, zoledronic acid, was assessed in a 12-month randomized controlled trial of 412 postmenopausal women who received 12 months of teriparatide 20 μg daily, a single infusion of zoledronic acid 5 mg or both [52]. As indicated in Table 18.1, while spine BMD increased more in the combination group at early time points, increases at 12 months were similar in the combination therapy and teriparatide groups. The two drugs together also demonstrated larger initial increases in hip BMD, though by 12 months the increases were similar in the combination therapy and zoledronic acid monotherapy groups. In a pattern that differs from the studies involving alendronate, in the groups receiving both zoledronic acid and teriparatide, while bone resorption (CTX) was suppressed initially, this suppression was not sustained after the first several months and serum CTX levels eventually increased to levels above the original baseline by the end of the 12-month treatment period.

Table 18.1 12-month changes in bone mineral density in three randomized combination therapies or randomized controlled trials

Study	Sample size	Regimen	Lumbar spine (%)	Total hip (%)
Black et al. [51]	119	PTH 1–84	6.3	0.3
	60	Alendronate	4.6	~3
	59	Both	6.1	1.9[b]
Cosman et al. [52]	138	Teriparatide	7.0	1.1[a]
	137	Zoledronic acid	4.4[a]	2.2
	137	Both	7.5	2.3
Tsai et al. [53]	31	Teriparatide	6.2	0.7
	33	Denosumab	5.5	2.5
	30	Both	9.1[a]	4.9[a]

[a]Differs significantly from the other two groups
[b]Differs significantly from PTH-(1-84)

Taken together, it appears that combining PTH analogs with bisphosphonates do not provide significant additive skeletal effects in postmenopausal osteoporotic women. The reasons for this lack of efficacy are currently unclear. Potential hypotheses to explain the apparent counteractive effects of bisphosphonates and PTH analogs are suggested by the observed changes in markers of bone resorption and formation in these studies. Bone turnover marker data suggest that bisphosphonates may blunt the effects of PTH analogs because of the key role that bone resorption plays mediating the anabolic effects of PTH analogs or the inability of bisphosphonates to fully inhibit PTH analog-induced bone resorption (or some combination of both mechanisms).

Combination of Denosumab and Teriparatide

Unlike bisphosphonate-containing combinations, the combination of teriparatide and the RANKL

inhibitor, denosumab increase BMD at the spine and hip at both 1 and 2 years more than either of the drug alone. In the Denosumab and Teriparatide Administration (DATA) trial, 94 osteoporotic postmenopausal women were randomized to receive teriparatide 20 mcg daily, denosumab 60 mg every 6 months, or both for 2 years. Combination treatment increased spine, total hip, and femoral neck BMD more than either group after both 12 and 24 months [53, 58] (Table 18.1, Fig. 18.1). Specifically, the combination of both agents increased spine, total hip, and femoral neck BMD by 12.9%, 6.3%, and 6.8%, respectively, increases that currently cannot be achieved with 2-year courses of any approved single drug [20, 60–64]. Areal BMD at the distal radius increased by slightly more than 2% in both the denosumab and combinations groups, and these increases differed significantly from the decrease of 1.7% observed in the teriparatide group.

In this same study, the effects of these interventions on bone microarchitecture and estimated were assessed by high-resolution peripheral QCT (HR-pQCT) [19]. Total volumetric bone mineral density (vBMD) at the radius and tibia, trabecular vBMD at the radius, and cortical vBMD at the tibia all increased more in women who received both drugs compared to either denosumab or teriparatide alone. Cortical thickness also increased more in the combination group than the other two groups, while cortical porosity increased in a fairly linear fashion over the entire 24-month treatment period in the teriparatide group but was stable in both other groups. Using the engineering technique of finite element analysis to estimate strength at both the radius and the tibia, the advantage of combination therapy is also apparent.

The pattern of changes in biochemical markers of bone resorption and formation induced by combined teriparatide/denosumab suggest a unique mechanism underlying the regimen's distinctive efficacy. As shown in the figure, bone resorption, as assessed by serum CTX, was identically suppressed in women treated with combination therapy and denosumab monotherapy during the initial 24 months of the trial, whereas the changes in bone formation markers differed, in that serum osteocalcin remained stable in the combination therapy group for the initial 3 months of treatment and then declined only modestly thereafter (though not to the level observed in the denosumab monotherapy group) [58]. This divergent pattern in bone resorption and formation marker changes in the combination group suggests that when given together, denosumab fully inhibits teriparatide-induced bone resorption but does not interfere with teriparatide-induced "modelling-based" bone formation (i.e., bone formation that does not require antecedent bone resorption).

In summary, while bisphosphonate-containing combinations with PTH analogs do not lead to additive effects, the combination of denosumab and teriparatide appears to be a promising approach. These rapid and large gains in BMD of the hip and spine suggest that this approach may be particularly useful in patients with severe osteoporosis in whom no single therapy can adequately reduce fracture risk. Larger studies assessing this regimen's capacity to reduce fracture incidence are now needed.

Sequential Approaches to Osteoporosis Therapy

Antiresorptive Agents After Osteoanabolic Agents

When teriparatide and abaloparatide are initiated, bone remodeling is rapidly stimulated but remodeling rates revert to pretreatment levels after 12–24 months of treatment [65]. Despite this pattern of bone cell activity, however, BMD continues to increase over the entire 2-year treatment period, likely due to continued modeling-based bone formation [66]. When PTH analogs are discontinued, BMD begins to revert to pretreatment levels almost immediately though studies have suggested that the antifracture efficacy is maintained for up to 18 months after the drug has been stopped [67, 68]. That said, it is likely that most of the beneficial effects of PTH analogs do eventually dissipate if they are not followed by a potent antiresorptive drug.

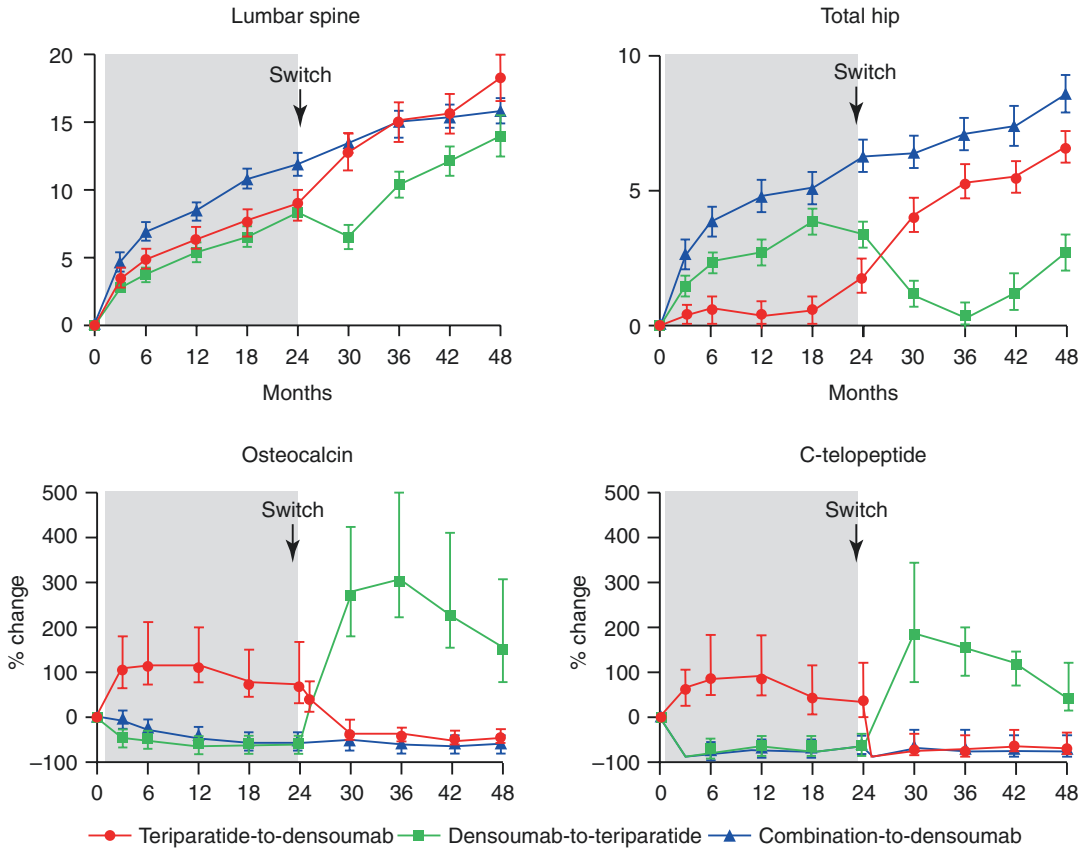

Fig. 18.1 Mean percent change (±SEM) in BMD at the spine and total hip and median percent change in osteocalcin and P1NP (±IQR) over the 48 months of the DATA and DATA-Switch studies. (Based on data from Refs. [53, 58, 59])

The capacity of oral alendronate to prevent post-teriparatide bone loss was studied in several clinical trials and is clearly effective not only consolidating the gains achieved with anabolic therapy but also in further increasing hip and spine BMD [69–71]. Similarly, patients who have been treated with 18-months of abaloparatide experience additional areal BMD gains and maintain a fracture-reduction benefit when switched to alendronate [61]. The selective estrogen receptor modulator, raloxifene, also prevents post-teriparatide bone loss but appears to be less effective than alendronate at further increasing BMD, particularly at the spine [72].

The ability of denosumab to further increase BMD when used after teriparatide was assessed using the *DATA-Switch* study (see Fig. 18.1). In DATA-Switch, postmenopausal women who received 2 years of teriparatide followed by 2 years of denosumab experienced large additional increases in both spine and hip BMD. Specifically, spine BMD increased by an additional 9.4% during the 2 years of denosumab (18.3% total 4 year increase) and total hip BMD increased by an additional 4.8% (6.6% total 4 year increase) [59]. Notably, these post-teriparatide denosumab-induced BMD increases appear to be significantly greater than what can be achieved with bisphosphonates therapy after teriparatide or when denosumab is administered to treat naïve patients [59, 73]. Denosumab was also able to further increase BMD in patients who previously received 2 years of combined teriparatide/denosumab therapy [59].

The skeletal effects of potent antiresorptive therapy, when used after the currently investigational mixed osteoanabolic/antiresorptive agent, romozosumab, have also been studied.

Romozosumab is a monoclonal antibody that inhibits osteocyte-derived sclerostin and has potent but transient osteoanabolic effects and weaker, but sustained, antiresorptive properties [74]. In these studies, denosumab was shown to further decrease bone resorption, augment gains in spine and hip areal BMD, and maintain antifracture efficacy when used after romozosumab [75, 76].

Osteoanabolic Agents After Antiresorptive Agents

Many patients who are treated with osteoanabolic drugs have already been exposed to antiresorptive agents, usually bisphosphonates, often for extended periods. Despite this common pattern of medication sequence, several clinical trials have clearly demonstrated that switching from a bisphosphonate to a PTH analog may result in transient cortical BMD loss and diminished BMD gains at sites of predominantly trabecular bone, such as the lumbar spine [56, 77–81]. For example, in a clinical trial of 59 postmenopausal osteoporotic women who previously received either alendronate or raloxifene for 18–36 months followed by 18-months of teriparatide, spine areal BMD increased more in those who had previously received raloxifene than those who had received alendronate and total hip areal BMD actually decreased by almost 2% in the initial 6 months of teriparatide therapy in those previously treated with alendronate [79]. In a separate study, 24 months of teriparatide was administered to postmenopausal women who were either treatment naïve or had prior bisphosphonate use and areal spine BMD increased more in the treatment-naïve group than those with prior bisphosphonate exposure [82]. This general pattern was also observed in several additional studies involving bisphosphonates [78–81], and blunting was suggested when romosozumab was given after bisphosphonate exposure as well [83].

The transition from denosumab to teriparatide appears to result in a uniquely maladaptive stimulation of high-turnover bone loss. In the DATA-Switch study previously described (Fig. 18.1), women who transitioned from denosumab to teriparatide experienced 6 months of declining areal BMD at the spine, 12 months of declining areal BMD at the hip and femoral neck, and progressive bone loss during all 24 months of treatment at the distal radius [59]. Moreover, at the distal tibia and distal radius, the transition from denosumab to teriparatide resulted in progressive decreases in total volumetric cortical volumetric BMD, progressive increases in cortical porosity, and reduced bone strength as assessed by finite element analysis [84]. Notably, this observed bone loss and deterioration of skeletal microarchitecture was associated with a dramatic stimulation of bone remodeling as serum markers of both bone formation and bone resorption increased by two- to threefold in the 6–12 months after the drug transition and remained elevated even 24 months after the drug transition [59]. This accelerated rate of bone remodeling, accompanied by bone loss, is concerning given that the more modest stimulation of bone turnover that occurs when denosumab is discontinued without a transition to teriparatide has been shown to be accompanied by a rapid and complete loss of denosumab's antifracture efficacy and an increase in the risk of multiple vertebral compression fractures, especially in those with very low BMD and prevalent fractures [85, 86].

Adding One Class of Osteoporosis Medication to Another

Several studies have assessed an overlapping medication approach to osteoporosis therapy. For example, in a clinical trial of 198 postmenopausal osteoporotic women, who initially received 18+ months of either alendronate or raloxifene, it was reported that in the prior-raloxifene group, switching to or adding teriparatide resulted in similar BMD increases, whereas in the prior-alendronate group, adding teriparatide increased spine BMD more than switching to teriparatide [80]. In a separate trial of 125 postmenopausal osteoporotic women who had received 9 months of teriparatide, adding raloxifene for 9 months resulted in larger spine BMD gains and adding alendronate resulted in larger hip BMD gains when compared

to continuing teriparatide alone [87]. Furthermore, in a 12-month extension to this study in which teriparatide was discontinued in all three groups, the greatest BMD increases occurred in the group that received 9 months of teriparatide followed by 9 months of combined teriparatide/alendronate followed by 12 months of alendronate monotherapy [88]. Finally, 126 osteoporotic women who had been taking alendronate for at least 1 year were randomized to 15 months of either continued alendronate plus teriparatide 20 μg daily, continued alendronate plus teriparatide for three 3-month cycles alternating with 3 months of alendronate alone or continuing alendronate alone. Areal BMD of the spine increased similarly in both groups who received teriparatide but did not increase further in the alendronate alone group, while hip BMD increased slightly and similarly in all three treatment groups [89].

Summary

In the past two decades, there has been a large expansion in osteoporosis treatment options, particularly in terms of the various antiresorptive drugs but also among osteoanabolic agents. This expansion has led to increased interest in developing combination and sequential drug approaches with the potential of providing greater benefit than monotherapy. The clinical trials completed to date have demonstrated that when given sequentially, it is preferable to first initiate osteoanabolic therapy and then transition to an antiresorptive agent as this approach leads to the greatest gains in bone mass and, in some circumstances, have been shown to reduce fracture risk in osteoporotic patients. These trials have also demonstrated that while prior bisphosphonate exposure may diminish the efficacy of subsequent PTH analog therapy, it is the specific transition from denosumab to teriparatide that should be unequivocally avoided due to rapid bone induced by accelerated skeletal metabolism—a physiologic state that may have significant negative clinical consequences. Studies assessing combined osteoanabolic/antiresorptive therapy have suggested that while the combination of bisphosphonates and PTH analogs does not result in clinical benefit, the combination of denosumab and teriparatide appears to be uniquely able to increase BMD and improve skeletal microarchitecture as compared to monotherapy. What is now required are larger studies that can adequately assess the comparative effectiveness of the various combination and sequential therapy approaches on clinically important endpoints in patients with established or severe osteoporosis.

References

1. Adler RA, El-Hajj Fuleihan G, Bauer DC, Camacho PM, Clarke BL, Clines GA, et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2016;31(1):16–35.
2. Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung AM, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2014;29(1):1–23.
3. Khan M, Cheung AM, Khan AA. Drug-related adverse events of osteoporosis therapy. Endocrinol Metab Clin N Am. 2017;46(1):181–92.
4. Gardella T. Interactions of PTH with receptors and signaling. In: Bilezikian J, editor. The parathyroids. 3rd ed. New York: Elsevier; 2015. p. 65–80.
5. Frolik CA, Black EC, Cain RL, Satterwhite JH, Brown-Augsburger PL, Sato M, et al. Anabolic and catabolic bone effects of human parathyroid hormone (1-34) are predicted by duration of hormone exposure. Bone. 2003;33(3):372–9.
6. Charles JF, Aliprantis AO. Osteoclasts: more than 'bone eaters'. Trends Mol Med. 2014;20(8):449–59.
7. Martin TJ. Bone biology and anabolic therapies for bone: current status and future prospects. J Bone Metabol. 2014;21(1):8–20.
8. Ferrandon S, Feinstein TN, Castro M, Wang B, Bouley R, Potts JT, et al. Sustained cyclic AMP production by parathyroid hormone receptor endocytosis. Nat Chem Biol. 2009;5(10):734–42.
9. Okazaki M, Ferrandon S, Vilardaga JP, Bouxsein ML, Potts JT Jr, Gardella TJ. Prolonged signaling at the parathyroid hormone receptor by peptide ligands targeted to a specific receptor conformation. Proc Natl Acad Sci U S A. 2008;105(43):16525–30.
10. Hattersley G, Dean T, Corbin BA, Bahar H, Gardella TJ. Binding selectivity of abaloparatide for PTH-type-1-receptor conformations and effects on downstream signaling. Endocrinology. 2016;157(1):141–9.
11. 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.
12. 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.
13. Nishiyama KK, Cohen A, Young P, Wang J, Lappe JM, Guo XE, et al. Teriparatide increases strength of the peripheral skeleton in premenopausal women with idiopathic osteoporosis: A pilot HR-pQCT study. J Clin Endocrinol Metab. 2014;99:2418.
14. Parfitt AM. Parathyroid hormone and periosteal bone expansion. J Bone Miner Res. 2002;17(10):1741–3.
15. Hansen S, Hauge EM, Beck Jensen JE, Brixen K. Differing effects of PTH 1-34, PTH 1-84, and zoledronic acid on bone microarchitecture and estimated strength in postmenopausal women with osteoporosis: an 18-month open-labeled observational study using HR-pQCT. J Bone Miner Res. 2013;28(4):736–45.
16. Macdonald HM, Nishiyama KK, Hanley DA, Boyd SK. Changes in trabecular and cortical bone microarchitecture at peripheral sites associated with 18 months of teriparatide therapy in postmenopausal women with osteoporosis. Osteoporos Int. 2011;22(1):357–62.
17. Keaveny TM, Donley DW, Hoffmann PF, Mitlak BH, Glass EV, San Martin JA. Effects of teriparatide and alendronate on vertebral strength as assessed by finite element modeling of QCT scans in women with osteoporosis. J Bone Miner Res. 2007;22(1):149–57.
18. Keaveny TM, McClung MR, Wan X, Kopperdahl DL, Mitlak BH, Krohn K. Femoral strength in osteoporotic women treated with teriparatide or alendronate. Bone. 2012;50(1):165–70.
19. Tsai JN, Uihlein AV, Burnett-Bowie SM, Neer RM, Derrico NP, Lee H, 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.
20. 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(19):1434–41.
21. Miller PD, Hattersley G, Riis BJ, Williams GC, Lau E, Russo LA, 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.
22. Greenspan SL, Bone HG, Ettinger MP, Hanley DA, Lindsay R, Zanchetta JR, 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.
23. Reszka AA, Rodan GA. Mechanism of action of bisphosphonates. Curr Osteoporos Rep. 2003;1(2):45–52.
24. Nancollas GH, Tang R, Phipps RJ, Henneman Z, Gulde S, Wu W, et al. Novel insights into actions of bisphosphonates on bone: differences in interactions with hydroxyapatite. Bone. 2006;38(5):617–27.
25. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361(8):756–65.
26. Lacey DL, Timms E, Tan HL, Kelley MJ, Dunstan CR, Burgess T, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell. 1998;93(2):165–76.
27. Boonen S, Ferrari S, Miller PD, Eriksen EF, Sambrook PN, Compston J, et al. Postmenopausal osteoporosis treatment with antiresorptives: effects of discontinuation or long-term continuation on bone turnover and fracture risk–a perspective. J Bone Miner Res. 2012;27(5):963–74.
28. Eastell R, Christiansen C, Grauer A, Kutilek S, Libanati C, McClung MR, et al. Effects of denosumab on bone turnover markers in postmenopausal osteoporosis. J Bone Miner Res. 2011;26(3):530–7.
29. Dempster DW, Zhou H, Recker RR, Brown JP, Recknor CP, Lewiecki EM, et al. Differential effects of teriparatide and denosumab on intact PTH and bone formation indices: AVA osteoporosis study. J Clin Endocrinol Metab. 2016;101(4):1353–63.
30. Brown JP, Reid IR, Wagman RB, Kendler D, Miller PD, Jensen JE, et al. Effects of up to 5 years of denosumab treatment on bone histology and histomorphometry: the FREEDOM study extension. J Bone Miner Res. 2014;29:2051.
31. Brown JP, Dempster DW, Ding B, Dent-Acosta R, San Martin J, Grauer A, et al. Bone remodeling in postmenopausal women who discontinued denosumab treatment: off-treatment biopsy study. J Bone Miner Res. 2011;26(11):2737–44.
32. Reid IR, Miller PD, Brown JP, Kendler DL, Fahrleitner-Pammer A, Valter I, et al. Effects of denosumab on bone histomorphometry: the FREEDOM and STAND studies. J Bone Miner Res. 2010;25(10):2256–65.
33. Streicher C, Heyny A, Andrukhova O, Haigl B, Slavic S, Schuler C, et al. Estrogen regulates Bone turnover by targeting RANKL expression in bone lining cells. Sci Rep. 2017;7(1):6460.
34. Drake MT, Khosla S. The role os sex steroids in the pathogenesis of osteoporosis. In: Rosen C, editor. Primer on the metabolic bone diseases and disorders of mineral metabolism. 8th ed. Ames: Wiley-Blackwell; 2013. p. 367–75.
35. Wasnich RD, Bagger YZ, Hosking DJ, McClung MR, Wu M, Mantz AM, et al. Changes in bone density and turnover after alendronate or estrogen withdrawal. Menopause. 2004;11(6 Pt 1):622–30.
36. Thomsen K, Riis BJ, Johansen JS, Christiansen C, Rodbro P. Bone turnover in postmenopausal women after withdrawal of estrogen/gestagen replacement therapy. Gynecol Endocrinol. 1987;1(2):169–75.
37. Sornay-Rendu E, Garnero P, Munoz F, Duboeuf F, Delmas PD. Effect of withdrawal of hormone replace-

ment therapy on bone mass and bone turnover: the OFELY study. Bone. 2003;33(1):159–66.
38. Bone HG, Greenspan SL, McKeever C, Bell N, Davidson M, Downs RW, et al. Alendronate and estrogen effects in postmenopausal women with low bone mineral density. Alendronate/Estrogen study group. J Clin Endocrinol Metab. 2000;85(2):720–6.
39. Greenspan SL, Resnick NM, Parker RA. Combination therapy with hormone replacement and alendronate for prevention of bone loss in elderly women: a randomized controlled trial. JAMA. 2003;289(19):2525–33.
40. Harris ST, Eriksen EF, Davidson M, Ettinger MP, Moffett AH Jr, Baylink DJ, et al. Effect of combined risedronate and hormone replacement therapies on bone mineral density in postmenopausal women. J Clin Endocrinol Metab. 2001;86(5):1890–7.
41. Lindsay R, Cosman F, Lobo RA, Walsh BW, Harris ST, Reagan JE, et al. Addition of alendronate to ongoing hormone replacement therapy in the treatment of osteoporosis: a randomized, controlled clinical trial. J Clin Endocrinol Metabol. 1999;84(9):3076–81.
42. Palomba S, Orio F Jr, Colao A, di Carlo C, Sena T, Lombardi G, et al. Effect of estrogen replacement plus low-dose alendronate treatment on bone density in surgically postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2002;87(4):1502–8.
43. Sanad Z, Ellakwa H, Desouky B. Comparison of alendronate and raloxifene in postmenopausal women with osteoporosis. Climacteric. 2011;14(3):369–77.
44. Tiras MB, Noyan V, Yildiz A, Yildirim M, Daya S. Effects of alendronate and hormone replacement therapy, alone or in combination, on bone mass in postmenopausal women with osteoporosis: a prospective, randomized study. Hum Reprod. 2000;15(10):2087–92.
45. Tseng LN, Sheu WH, Ho ES, Lan HH, Hu CC, Kao CH. Effects of alendronate combined with hormone replacement therapy on osteoporotic postmenopausal Chinese women. Metabolism. 2006;55(6):741–7.
46. Wimalawansa SJ. Combined therapy with estrogen and etidronate has an additive effect on bone mineral density in the hip and vertebrae: four-year randomized study. Am J Med. 1995;99(1):36–42.
47. Lindsay R, Nieves J, Formica C, Henneman E, Woelfert L, Shen V, et al. Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. Lancet. 1997;350(9077):550–5.
48. Ste-Marie LG, Schwartz SL, Hossain A, Desaiah D, Gaich GA. Effect of teriparatide [rhPTH(1-34)] on BMD when given to postmenopausal women receiving hormone replacement therapy. J Bone Miner Res. 2006;21(2):283–91.
49. Cosman F, Nieves J, Woelfert L, Formica C, Gordon S, Shen V, 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.
50. Deal C, Omizo M, Schwartz EN, Eriksen EF, Cantor P, Wang J, et al. Combination teriparatide and raloxifene therapy for postmenopausal osteoporosis: results from a 6-month double-blind placebo-controlled trial. J Bone Miner Res. 2005;20(11):1905–11.
51. Black DM, Greenspan SL, Ensrud KE, Palermo L, McGowan JA, Lang TF, et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. N Engl J Med. 2003;349(13):1207–15.
52. Cosman F, Eriksen EF, Recknor C, Miller PD, Guanabens N, Kasperk C, et al. Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1-34)] in postmenopausal osteoporosis. J Bone Miner Res. 2011;26(3):503–11.
53. Tsai JN, Uihlein AV, Lee H, Kumbhani R, Siwila-Sackman E, McKay EA, et al. Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. Lancet. 2013;382(9886):50–6.
54. Uihlein AV, Leder BZ. Anabolic therapies for osteoporosis. Endocrinol Metab Clin N Am. 2012;41(3):507–25.
55. Finkelstein JS, Leder BZ, Burnett SM, Wyland JJ, Lee H, de la Paz AV, et al. Effects of teriparatide, alendronate, or both on bone turnover in osteoporotic men. J Clin Endocrinol Metab. 2006;91(8):2882–7.
56. Finkelstein JS, Wyland JJ, Lee H, Neer RM. Effects of teriparatide, alendronate, or both in women with postmenopausal osteoporosis. J Clin Endocrinol Metab. 2010;95(4):1838–45.
57. Schafer AL, Sellmeyer DE, Palermo L, Hietpas J, Eastell R, Shoback DM, et al. Six months of parathyroid hormone (1-84) administered concurrently versus sequentially with monthly ibandronate over two years: the PTH and ibandronate combination study (PICS) randomized trial. J Clin Endocrinol Metab. 2012;97(10):3522–9.
58. Leder BZ, Tsai JN, Uihlein AV, Burnett-Bowie SA, Zhu Y, Foley K, 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.
59. Leder BZ, Tsai JN, Uihlein AV, Wallace PM, Lee H, Neer RM, 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.
60. Bolognese MA, Teglbjaerg CS, Zanchetta JR, Lippuner K, McClung MR, Brandi ML, et al. Denosumab significantly increases DXA BMD at both trabecular and cortical sites: results from the FREEDOM study. J Clin Densitom. 2012;16(2):147–53.
61. Cosman F, Miller PD, Williams GC, Hattersley G, Hu MY, Valter I, et al. Eighteen months of treatment with subcutaneous abaloparatide followed by 6 months of treatment with alendronate in postmenopausal women with osteoporosis: Results of the ACTIVExtend Trial. Mayo Clin Proc. 2017;92(2):200–10.

62. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, 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.
63. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, 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.
64. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA. 1999;282(7):637–45.
65. Leder BZ, O'Dea LS, Zanchetta JR, Kumar P, Banks K, McKay K, et al. Effects of abaloparatide, a human parathyroid hormone-related peptide analog, on bone mineral density in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2015;100(2):697–706.
66. Dempster DW, Zhou H, Recker RR, Brown JP, Bolognese MA, Recknor CP, 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.
67. Leder BZ, Neer RM, Wyland JJ, Lee HW, Burnett-Bowie SM, Finkelstein JS. Effects of teriparatide treatment and discontinuation in postmenopausal women and eugonadal men with osteoporosis. J Clin Endocrinol Metab. 2009;94(8):2915–21.
68. Lindsay R, Scheele WH, Neer R, Pohl G, Adami S, Mautalen C, et al. Sustained vertebral fracture risk reduction after withdrawal of teriparatide in postmenopausal women with osteoporosis. Arch Intern Med. 2004;164(18):2024–30.
69. Rittmaster RS, Bolognese M, Ettinger MP, Hanley DA, Hodsman AB, Kendler DL, et al. Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate. J Clin Endocrinol Metab. 2000;85(6):2129–34.
70. Kurland ES, Heller SL, Diamond B, McMahon DJ, Cosman F, Bilezikian JP. The importance of bisphosphonate therapy in maintaining bone mass in men after therapy with teriparatide [human parathyroid hormone(1-34)]. Osteoporos Int. 2004;15(12):992–7.
71. Black DM, Bilezikian JP, Ensrud KE, Greenspan SL, Palermo L, Hue T, 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.
72. Eastell R, Nickelsen T, Marin F, Barker C, Hadji P, Farrerons J, 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.
73. Ebina K, Hashimoto J, Kashii M, Hirao M, Kaneshiro S, Noguchi T, et al. The effects of switching daily teriparatide to oral bisphosphonates or denosumab in patients with primary osteoporosis. J Bone Miner Metab. 2017;35(1):91–8.
74. McClung MR, Grauer A, Boonen S, Bolognese MA, Brown JP, Diez-Perez A, et al. Romosozumab in postmenopausal women with low bone mineral density. N Engl J Med. 2014;370(5):412–20.
75. McClung MR, Brown JP, Diez-Perez A, Resch H, Caminis J, Meisner P, et al. Effects of 24 months of treatment with romosozumab followed by 12 months of denosumab or placebo in postmenopausal women with low bone mineral density: a randomized, double-blind, phase 2, parallel group study. J Bone Miner Res. 2018;33:1397.
76. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, et al. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med. 2016;375(16):1532–43.
77. Finkelstein JS, Hayes A, Hunzelman JL, Wyland JJ, Lee H, Neer RM. The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. N Engl J Med. 2003;349(13):1216–26.
78. Boonen S, Marin F, Obermayer-Pietsch B, Simoes ME, Barker C, Glass EV, 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.
79. 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.
80. Cosman F, Wermers RA, Recknor C, Mauck KF, Xie L, Glass EV, 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.
81. Miller PD, Delmas PD, Lindsay R, Watts NB, Luckey M, Adachi J, 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.
82. Obermayer-Pietsch BM, Marin F, McCloskey EV, Hadji P, Farrerons J, Boonen S, 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 Off J Am Soc Bone Miner Res. 2008;23(10):1591–600.
83. Langdahl BL, Libanati C, Crittenden DB, Bolognese MA, Brown JP, Daizadeh NS, et al. Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy:

a randomised, open-label, phase 3 trial. Lancet. 2017;390(10102):1585–94.
84. Tsai JN, Nishiyama KK, Lin D, Yuan A, Lee H, Bouxsein ML, et al. Effects of denosumab and teriparatide transitions on bone microarchitecture and estimated strength: the DATA-switch HR-pQCT study. J Bone Miner Res Off J Am Soc Bone Miner Res. 2017;32(10):2001–9.
85. Bone HG, Bolognese MA, Yuen CK, Kendler DL, Miller PD, Yang YC, et al. Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. J Clin Endocrinol Metab. 2011;96(4):972–80.
86. Cummings SR, Ferrari S, Eastell R, Gilchrist N, Jensen JB, McClung M, et al. Vertebral fractures after discontinuation of denosumab: a post hoc analysis of the randomized placebo-controlled FREEDOM trial and its extension. J Bone Miner Res. 2018;33(2):190.
87. Muschitz C, Kocijan R, Fahrleitner-Pammer A, Lung S, Resch H. Antiresorptives overlapping ongoing teriparatide treatment result in additional increases in bone mineral density. J Bone Miner Res. 2013;28(1):196–205.
88. Muschitz C, Kocijan R, Fahrleitner-Pammer A, Pavo I, Haschka J, Schima W, et al. Overlapping and continued alendronate or raloxifene administration in patients on teriparatide: effects on areal and volumetric bone mineral density–the CONFORS study. J Bone Miner Res Off J Am Soc Bone Miner Res. 2014;29(8):1777–85.
89. Cosman F, Nieves J, Zion M, Woelfert L, Luckey M, Lindsay R. Daily and cyclic parathyroid hormone in women receiving alendronate. N Engl J Med. 2005;353(6):566–75.