ISSN 2472-1972

Osteoanabolic Agents for Osteoporosis

Andrea V. Haas[1] and Meryl S. LeBoff[1]

[1]*Division of Endocrinology, Diabetes, and Hypertension, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115*

Medications for osteoporosis are classified as either antiresorptive or anabolic. Whereas antiresorptive agents prevent bone resorption, anabolic agents promote new bone formation. Anabolics should be considered in individuals with severe osteoporosis, failure of alternative osteoporosis agents, intolerability or contraindications to other osteoporosis agents, and glucocorticoid-induced osteoporosis. There are currently two approved anabolic therapies, teriparatide and abaloparatide, and a third anabolic agent, romozosumab, is under review by the US Food and Drug Administration. Teriparatide and abaloparatide are administered as daily subcutaneous injections and have been shown to reduce vertebral and nonvertebral fractures significantly. The most common side effects are headache and nausea, but teriparatide and abaloparatide are generally well tolerated. The sequence of administration of anabolic therapy is important. Benefits of anabolics are attenuated in individuals with prior antiresorptive exposure; however, antiresorptive agents administered after anabolics consolidate bone mineral density gains.

Freeform/Key Words: abaloparatide, anabolic, bone mineral density, fracture, romosozumab, teriparatide

Osteoporosis is a major and growing public health concern. Approximately one in two women and one in five men, aged 50 and older, will experience an osteoporotic fracture [1]. Fractures are associated with reduced independence, increased risk of future fractures, and increased morbidity and mortality [2, 3]. Effective prevention and treatment of osteoporosis and fractures are of paramount importance.

The overarching goal of treating osteoporotic patients is to prevent incidence of fractures. Osteoporosis treatment is achieved through either inhibition of bone resorption and/or stimulation of bone formation. To date, antiresorptive agents (*e.g.*, bisphosphonates, denosumab, estrogen, and raloxifene) are the most commonly used therapies for the treatment of osteoporosis. Through diverse mechanisms, antiresorptive agents suppress osteoclastic-mediated bone breakdown and bone turnover [4]. Conversely, osteoanabolic agents promote new bone formation by activation of osteoblasts and bone remodeling [5].

Teriparatide and abaloparatide are currently the only two approved anabolic agents for the treatment of osteoporosis in the United States. The US Food and Drug Administration (FDA) approved teriparatide in 2002 and abaloparatide in 2017. Both agents reduce the incidence of vertebral and nonvertebral fractures [6, 7]. A third agent, romosozumab, has remained under evaluation by the FDA, given concerns regarding increased cardiovascular events [8].

The aims of this review are to discuss the mechanism of action, clinical use, and major clinical studies of anabolic drugs for the treatment of osteoporosis. Relevant studies were selected after a PubMed search through December 2017 and included at least one of the following keywords: anabolic, bone mineral density (BMD), fracture, teriparatide, abaloparatide, and romosozumab.

Abbreviations: ACTIVE, Abaloparatide Comparator Trial in Vertebral Endpoints; BMD, bone mineral density; FDA, US Food and Drug Administration; FRAME, Fracture Study in Postmenopausal Women with Osteoporosis; PTH1R, PTH 1 receptor.

Received 20 April 2018
Accepted 3 July 2018
First Published Online 9 July 2018

Articles of potential interest were then reviewed in full. Additional articles were identified from those publications' references.

1. Mechanism of Action

PTH and PTHrP are encoded by related genes and bind to the same receptor, PTH 1 receptor (PTH1R) [9]. PTH (1-84) is an 84-amino acid polypeptide, and PTHrP (1-34) is a 34-amino acid polypeptide. PTH is secreted by the parathyroid gland and plays a fundamental role in calcium homeostasis. PTH increases serum calcium concentrations via promotion of osteoclast-mediated calcium release from bone, distal renal tubular calcium reabsorption, and intestinal calcium absorption. PTHrP is produced by many different tissues and exerts its effects via paracrine actions. Like PTH, PTHrP stimulates bone resorption and renal tubular calcium reabsorption, but in contrast to PTH, PTHrP plays a minor, if any, role in intestinal calcium absorption. PTHrP is additionally involved in fetal calcium regulation, placental calcium transfer, and lactation [10, 11].

Teriparatide and abaloparatide, like PTH and PTHrP, enact their effects via binding to PTH1R. Teriparatide, recombinant human PTH [PTH (1-34)], comprises the first 34 amino acids of the *N*-terminal end of PTH. Abaloparatide [PTHrP (1-34)] is a 34-amino acid synthetic analog of PTHrP that is identical to PTHrP at amino acids 1-22 but differs in amino acids 23-34. These differences were intentionally constructed to maximize the stability and anabolic activity of abaloparatide [12]. Abaloparatide shares 76% homology with PTHrP and 41% homology with PTH [12].

Whereas continuous exposure to PTH or PTHrP results in increased bone resorption, intermittent administration of PTH (1-34) or PTHrP (1-34) leads to an anabolic window and enhanced bone formation [13]. To date, it is not completely understood why the continuous vs intermittent exposure to PTH/PTHrP causes differing effects on bone.

PTH1R has two conformations: RG and R0. The RG conformation results in a shorter intracellular signaling response than the R0 conformation and is believed to result in more anabolic activity. Abaloparatide has a higher selectivity for the RG and a lower selectivity for the R0 conformation than teriparatide and has been hypothesized to have more potent effects on bone formation with lesser effects on bone resorption and lower rates of inducing hypercalcemia [7, 9].

2. Clinical Use, Dosing, and Monitoring

Osteoanabolic treatment should be considered in four main groups of individuals: (1) severe osteoporosis or high risk of fracture, (2) failure of alternative osteoporosis agents while adherent to treatment (fracture or loss of BMD), (3) intolerability or contraindications to other osteoporosis agents, and (4) glucocorticoid-induced osteoporosis [6, 7, 14–16]. Available data discussed below show that anabolic therapies produce greater increases in bone density when they are administered before antiresorptive medications. However, anabolic agents are not generally advocated as the first line for the treatment of osteoporosis, given their substantial cost.

Before the commencement of anabolic agents, it is important to exclude secondary causes of osteoporosis, and it is prudent to obtain serum calcium, albumin, phosphorus, creatinine, alkaline phosphatase, and 25-hydroxyvitamin D levels. Treatment with PTH/PTHrP analogs is contraindicated in patients with hypercalcemic disorders. PTH/PTHrP analogs should additionally not be used in anyone with primary or secondary hyperparathyroidism or anyone at increased risk for osteosarcoma (*e.g.*, history of Paget disease, radiation involving the skeleton, bone metastases). PTH/PTHrP analogs should be avoided in individuals with a history of renal stones. It is recommended to assess for underlying hypercalciuria with a 24-hour urine calcium (urinary calcium excretion >400 mg/24 h), as both teriparatide and abaloparatide can exacerbate hypercalciuria [7]. Patients who are vitamin D deficient should be replaced until vitamin D stores are ≥30 ng/dL before initiation of treatment.

Teriparatide [PTH (1-34)] is administered as a 20-μg daily subcutaneous injection into the thigh or abdomen. A 28-dose, prefilled pen is available and requires refrigeration. The 2017 *Institute for Clinical and Economic Review* quoted the wholesale acquisition cost of one pen of teriparatide at $2998, with an annual cost of $35,976, although discounts of 30% to 40% were possible [17]. Abaloparatide [PTHrP (1-34)] is administered as an 80-μg daily subcutaneous injection into the periumbilical region. Abaloparatide is available in a 30-dose, prefilled pen, which in contrast, does not require refrigeration between doses. The 2017 wholesale acquisition cost of one pen of abaloparatide was ~$1625, with an annual cost of $19,500, although again, discounts were possible [17]. Teriparatide and abaloparatide are also being evaluated for transdermal application [12]. The initial dose of both teriparatide and abaloparatide should be given with the patient sitting or lying in a monitored setting in the event of orthostatic hypotension. Thereafter, the patient can self-administer injections at home.

There are currently no official guidelines on monitoring for the development of hypercalcemia. Importantly, serum calcium should be drawn 24 hours after the last injection. If hypercalcemia does develop, then the first step is reduction in calcium and/or vitamin D supplementation. If hypercalcemia persists (serum calcium >11.0 mg/dL), then anabolic dosing can be adjusted to every other day, and if it still present, PTH/PTHrP treatment should be discontinued. Likewise, there is no consensus on frequency of BMD monitoring, but dual energy x-ray absorptiometry is typically performed at the start of treatment and again after 1 to 2 years on therapy.

Cumulative use of abaloparatide and teriparatide is restricted to a maximum of 2 years. Use is limited, given that clinical trials did not exceed 2 years, as well as concerns regarding the theoretical risk of increased rates of osteosarcoma observed in rodent models.

3. Clinical Efficacy of Teriparatide

The seminal 2001 Fracture Prevention Trial demonstrated that treatment with teriparatide treatment of at least 18 months significantly reduced the risk of vertebral and nonvertebral fractures in postmenopausal women with osteoporosis. The trial randomized 1637 postmenopausal women with a previous vertebral fracture to a subcutaneous injection of teriparatide 20 μg/d, teriparatide 40 μg/d, or placebo [6]. The study was terminated early, at 21 months, to investigate concerns regarding development of osteosarcomas in Fischer rats during a toxicology study, although no increased risk in humans has been found [18–20]. After 18 months, treatment with teriparatide resulted in dose-dependent increases in BMD at the spine and hip. Notably, BMD, at the distal radius and shaft of the radius, actually decreased with teriparatide. Both the 20- and 40-μg/d doses of teriparatide resulted in reduced rates of vertebral fractures. There was a 4% incidence of vertebral fracture in the teriparatide 20-μg/d group, 5% in the teriparatide 40-μg/d group, and 14% in the placebo group, representing a risk reduction of 65% in the teriparatide 20-μg group and 69% in the teriparatide 40-μg group compared with placebo. Nonvertebral fractures occurred in 3% in each of the teriparatide groups vs 6% in the placebo group, a risk reduction of 53% in the teriparatide 20-μg group and 54% in the teriparatide 40-μg group compared with placebo [6]. Of note, Kaplan-Meier incidence curves for nonvertebral fracture did not begin to diverge between teriparatide and placebo until 9 to 10 months into treatment [6]. There was no statistically significant difference in fracture reduction between the two doses of teriparatide, but higher rates of hypercalcemia developed at the 40-μg/d dose [6].

Teriparatide has also shown efficacy in osteoporotic men. Men (437) with low spine or hip BMD were randomized to daily injections of teriparatide 20 μg, teriparatide 40 μg, or placebo. The study was also stopped early, after a median duration of 11 months, because of the development of osteosarcomas in rats. At the end of follow-up, spine BMD increased by 5.9% and 9% above baseline in the 20- and 40-μg groups, respectively, and femoral neck BMD increased by 1.5% and 2.9% above baseline in the 20- and 40-μg groups, respectively [21].

Additionally, teriparatide is effective for glucocorticoid-induced osteoporosis. In a 36-month, randomized, controlled trial, 428 men and women with osteoporosis, who had

received ≥5 mg/d of a prednisone equivalent for ≥3 months, were randomized to either teriparatide or alendronate. Mean BMD at the lumbar spine increased more (11% vs 5.3%), and fewer new vertebral fractures occurred (1.7% vs 7.7%) in the teriparatide group than in the alendronate group [14].

4. Clinical Efficacy of Abaloparatide

A phase 2, 24-week trial randomized 222 postmenopausal women with osteoporosis to abaloparatide 20, 40, or 80 μg/d, teriparatide 20 μg/d, or placebo. Abaloparatide, at both the 40- and 80-μg doses significantly increased BMD at the lumbar spine, femoral neck, and total hip compared with placebo. Radius BMD was not reported. No statistically significant difference in lumbar spine BMD was noted between teriparatide and abaloparatide. In contrast, substantial improvements in total hip BMD were seen with abaloparatide compared with teriparatide [22].

In the phase 3 Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE) trial, 2463 postmenopausal women were randomized to 18 months of daily subcutaneous injections of abaloparatide 80 μg, open-label teriparatide 20 μg, or placebo. Participants were aged 49 to 86 years and had either BMD T-scores of −3.0 or below or a history of fractures with a BMD T-score of −2.5 or below. Vertebral fractures occurred in 0.58% of participants in the abaloparatide group and in 4.22% in the placebo group, a risk reduction in the abaloparatide group of 86%. Nonvertebral fractures occurred in 2.7% in the abaloparatide group compared with 4.7% in the placebo group, a difference that just met statistical significance. Whereas not a primary endpoint, no statistically significant difference in vertebral fractures was found between teriparatide and abaloparatide [7].

5. Clinical Efficacy of Romosozumab

Romosozumab is currently under review by the FDA for approval. Romosozumab was developed after the 2001 finding that sclerosteosis, a rare genetic disorder with high bone mass, was associated with a loss-of-function mutation in the SOST gene that encodes sclerostin [23]. Sclerostin is produced by osteocytes and both inhibits bone formation and enhances bone resorption. Romosozumab is a humanized monoclonal antibody to sclerostin. The phase 3 Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) trial randomized 7180 subjects to monthly subcutaneous injections of romosozumab 210 mg or placebo for 12 months, followed by an additional 12 months of denosumab in both groups. Participants were women, 55 to 90 years of age with BMD T-scores between −3.0 and −5.0. After 12 months of treatment with romosozumab or placebo, new vertebral fractures occurred in 0.5% of women in the romosozumab group and 1.8% of women in the placebo group, representing a risk reduction of 75% [24].

In the Active-Controlled FRAME at High Risk, 4093 postmenopausal women with osteoporosis and a fragility fracture were randomly assigned to receive monthly subcutaneous romosozumab or weekly oral alendronate for 12 months, followed by alendronate for 12 months in both groups. Over a period of 24 months, new vertebral fractures occurred 6.2% in the romosozumab-to-alendronate group compared with 11.9% in the alendronate-to-alendronate group, representing a 48% lower risk of new vertebral fractures in the romosozumab-to-alendronate group. There was a 27% lower risk of clinical fractures and 38% lower risk of hip fractures. However, during year one, serious cardiovascular adverse events were observed more often with romosozumab than with alendronate [8]. Fifty patients (2.5%) in the romosozumab group and 38 patients (1.9%) in the alendronate group had adjudicated serious cardiovascular adverse events. This contrasts with the FRAME trial, where the incidence of cardiovascular events was balanced between the groups [8]. One possible explanation could be a role for sclerostin in aortic vascular smooth muscle, as some studies have shown SOST expression [25]. Given concerns for increased cardiovascular events, approval for romosozumab remains pending.

6. Head-to-Head Comparisons

There have been very few trials that have compared one anabolic agent with another or an anabolic with an antiresorptive (Table 1). A study from Langdahl *et al.* [26], published in 2017, compared changes in BMD after 12 months of romosozumab or teriparatide in women with postmenopausal osteoporosis who had previously received at least 3 years of bisphosphonate therapy. Mean percentage changes in areal BMD from baseline at the total hip, femoral neck, and lumbar spine were significantly greater in the romosozumab group than in the teriparatide group at both 6 and 12 months. At 12 months, those in the romosozumab group had gained 2.9% in BMD at the total hip, 3.2% at the femoral neck, and 9.8% at the lumbar spine compared with −0.5% at the total hip, −0.2% at the femoral neck, and 5.4% at the lumbar spine for those randomized to teriparatide [26]. The ACTIVE trial randomized participants to abaloparatide, open-label teriparatide, or placebo. Whereas the primary outcome compared abaloparatide with placebo, a secondary outcome compared rates of nonvertebral fractures with abaloparatide and teriparatide. There were nonvertebral fractures in 2.7% in the abaloparatide group compared with 3.3% in the teriparatide group, but this difference did not reach statistical significance [7]. An exploratory end-point showed greater improvements in BMD with abaloparatide than those with teriparatide at the total hip and femoral neck at 6, 12, and 18 months and at the lumbar spine at 6 and 12 months but not at 18 months [7].

Table 1. Major Trials in Osteoanabolic Treatment

Trial Name	Study Population	Study Drugs	Fracture Reduction
Fracture Prevention Trial [6]	Postmenopausal women (1637) with ≥1 vertebral fractures	(1) Teriparatide 20 μg/d, (2) teriparatide 40 μg/d, or (3) placebo ×21 mo	Vertebral fractures occurred in 4% in the teriparatide 20 μg/d, 5% in the teriparatide 40 μg/d, and 14% in the placebo group, representing a risk reduction of 65% in teriparatide 20 μg group and 69% in teriparatide 40 μg group compared with placebo. Nonvertebral fractures occurred in 3% in each of the teriparatide groups vs 6% in the placebo group. Nonvertebral fracture risk reduction of 53% and 54% in 20 μg and 40 μg groups, respectively.
ACTIVE [7]	Postmenopausal women (2463) with T-score ≤−2.5 or T-score ≤−2.0 and ≥2 mild or ≥1 moderate vertebral or nonvertebral fracture	(1) Abaloparatide 80 μg/d, (2) teriparatide (open label) 20 μg/d, or (3) placebo ×18 mo	Vertebral fractures occurred in 0.58% in the abaloparatide group and 4.22% in the placebo group, a risk reduction of 86%. Nonvertebral fractures occurred in 2.7% in the abaloparatide group compared with 4.7% in the placebo group, a risk reduction of 43%.
Romosozumab Treatment in FRAME [24]	Postmenopausal women (7180) with T-score −2.5 to −3.5 at hip or spine	(1) Romosozumab 210 mg monthly or (2) placebo ×12 mo, followed by denosumab 60 mg every 6 mo ×12 mo in both groups	New vertebral fractures occurred in 0.5% of women in the romosozumab group and 1.8% of women in the placebo group. Risk reduction of 75% in vertebral fractures and no substantial risk reduction in nonvertebral fractures compared with placebo.

Whereas there have been only a few studies comparing anabolic with antiresorptive treatment, anabolic treatment was generally superior. New vertebral fractures were the primary outcome of the study, Effects of Teriparatide and Risedronate on New Fractures in Post-Menopausal Women with Severe Osteoporosis (VERO) (see Kendler *et al.* [27]). Among postmenopausal women with severe osteoporosis, risk of new vertebral fractures was significantly lower in those who received teriparatide (5.4%) than risedronate (12%), whereas nonvertebral fracture incidence was not statistically different [27]. Romosozumab was directly compared with alendronate in the Active-Controlled FRAME at High Risk. In postmenopausal women with osteoporosis, who were high risk for fracture, romosozumab treatment of 12 months, followed by alendronate, resulted in a significantly lower risk of vertebral and nonvertebral fractures than alendronate alone [8]. Teriparatide was compared with alendronate for treatment of glucocorticoid-induced osteoporosis, and teriparatide resulted in greater increases in BMD and fewer new vertebral fractures than alendronate [14].

7. Safety and Tolerability

Overall, teriparatide and abaloparatide are well tolerated. However, there are no long-term safety data with abaloparatide. Hypercalcemia and hypercalciuria are the two most common side-effects, although clinically substantial elevations rarely occur [6, 7].

In the 2001 Fracture Prevention Trial, teriparatide compared with placebo resulted in greater dizziness (9% vs 6%), leg cramps (3% vs 1%), and hypercalcemia (11% vs 2%) [6, 28]. The majority of incidences of hypercalcemia were <1 mg/dL above the laboratory's reference range. Women who did not develop hypercalcemia within the first 6 months of teriparatide seldom developed hypercalcemia thereafter. Orthostatic hypotension rarely occurred after the initial dose [6].

In a phase 2 trial among 222 postmenopausal women, abaloparatide was well tolerated. The incidence of headache (14% vs 7%) and dizziness (9% vs 4%) was slightly higher in the abaloparatide 80-μg group compared with placebo. Abaloparatide had a significantly lower incidence of hypercalcemia compared with teriparatide [22]. In the phase 3 ACTIVE trial of abaloparatide, the most common adverse events leading to study drug discontinuation were nausea (1.6%), dizziness (1.2%), and headache (1.0%). Again, the frequency of hypercalcemia was lower for abaloparatide than teriparatide (3.4% vs 6.4%) [7]. Increases in uric acid have also been demonstrated with use of both teriparatide and abaloparatide [29].

The most concerning adverse event is the theoretical increased risk of osteosarcoma. Teriparatide and abaloparatide carry a black-box warning for risk of osteosarcoma. This black-box warning derives from evidence that a higher proportion of Fischer rats that was administered PTH (1-34) from 8 weeks to 2 years of age at doses 4 to 28 times human exposure developed higher rates of osteosarcoma [18, 19]. The occurrence of osteosarcoma was dose dependent, and the tumors developed after PTH (1-34) had already induced osteosclerosis. In prior studies involving nearly 1000 humans, treatment with PTH (1-84), PTH (1-34), or PTH (1-38) for up to 3 years did not increase the incidence of bone tumors [20]. Furthermore, no relationship has been demonstrated between elevated PTH in the context of hyperparathyroidism and the occurrence of osteosarcoma in humans [30]. There have only been three reported cases of osteosarcoma among the more than one million worldwide patients who have received teriparatide, a rate that does not exceed the expected incidence of osteosarcoma in the general population [31].

8. Combination Therapy With Anabolics

Studies that combine teriparatide and bisphosphonates have generated inconsistent results. Most have demonstrated no additional benefit of combination teriparatide with bisphosphonates and have even shown some blunting of the anabolic response to PTH [29, 32,

33]. However, one study, combining a single dose of zoledronic acid with a daily injection of teriparatide, increased spine and hip BMD more than either agent alone [33].

The Denosumab and Teriparatide Administration study evaluated the efficacy of the combination denosumab and teriparatide over denosumab or teriparatide monotherapy. Denosumab is a monoclonal antibody that blocks the binding of receptor activator of nuclear factor κB ligand to its receptor, an interaction that is required for osteoclast formation, activation, and survival [34]. One hundred postmenopausal women with osteoporosis were assigned to receive teriparatide 20 μg/d, denosumab 60 mg every 6 months, or both. After 12 months, BMD at the lumbar spine increased more in the combination group (9.1%) than either the teriparatide (6.2%) or denosumab (5.5%) group alone. Femoral neck and total hip BMD also increased more in the combination group. Although at present, there are no data on fracture outcomes, teriparatide and denosumab administered together could be useful to treat patients at highest risk of fracture [35].

9. Sequence of Anabolic Therapy

The sequence in which anabolic and antiresorptive therapies are instituted impacts the skeletal response. Alendronate given before and concurrently with teriparatide attenuated the BMD and bone-turnover improvement compared with those who received teriparatide alone [36]. However, antiresorptive therapy, administered after an anabolic agent, consolidated the anabolic bone density gains. In the absence of subsequent antiresorptive treatment, BMD benefits will gradually wane, as bone loss has been reported to decline at a rate of up to 4% per year [37, 38]. With the use of alendronate or denosumab after teriparatide treatment, BMD benefits persisted or increased [39–41].

In the preplanned extension of the Denosumab and Teriparatide Administration trial, women who were originally assigned to 24 months of teriparatide received 24 months of denosumab, women who originally received 24 months of denosumab received 24 months of teriparatide, and women who initially received both drugs received an additional 24 months of denosumab alone. The switch from teriparatide or combination therapy to denosumab further increased BMD, whereas the switch from denosumab to teriparatide resulted in a transient loss of BMD and bone microarchitecture [42]. This raises concern for the use of teriparatide after denosumab and suggests that the combination of teriparatide and denosumab, followed by denosumab alone, may be the most potent treatment of severe osteoporosis.

The ACTIVExtend trial, an extension of ACTIVE, enrolled patients who completed 18 months of abaloparatide or placebo to receive up to 24 months of weekly alendronate. The extension trial is still ongoing, but the 6-month follow-up results reported that use of abaloparatide, followed by alendronate, further improved BMD and reduced fracture risk, although the absolute number of fractures was small [43]. These findings suggest that alendronate therapy can preserve the fracture-reduction benefits of abaloparatide.

10. Fracture Healing

There is growing evidence to suggest a role for teriparatide in the management of fracture healing. Teriparatide is not currently FDA approved for the treatment of fracture healing but has been used “off license” by many clinicians. There are numerous preclinical studies that have demonstrated that PTH enhances fracture healing [44–47]. However, the sparse, randomized, controlled human studies have been conflicting. In a randomized, controlled, pilot study in 12 premenopausal women with lower extremity stress fractures, teriparatide vs placebo for 8 weeks produced a substantial anabolic window, and more women on teriparatide (83.3%) vs placebo (57.1%) had improved or healed stress fractures, but this latter difference was not statistically significant [48]. A prospective, randomized, double-blind study of 102 postmenopausal women who had undergone conservative management of distal radial fractures showed shorter time to healing after administration of teriparatide

20 μg/d compared with placebo (9.1 vs 7.4 weeks), although there was no substantial difference between the teriparatide 40-μg/d dose and placebo [49]. An additional study among 40 women with proximal humerus fractures observed no improvement in fracture-healing time with teriparatide [50]. Further studies are needed to assess the efficacy of teriparatide or abaloparatide in the setting of fracture healing.

11. Conclusions

Anabolic agents are highly effective at increasing BMD and reducing incidence of both vertebral and nonvertebral fractures. Currently, teriparatide [PTH (1-34)] and abaloparatide [PTHrP (1-34)] are the only two approved anabolic agents, although at the time of this publication, a third agent, romosozumab, is under review by the FDA. Anabolic therapy is recommended for severe cases of osteoporosis or when alternative options are not available or not tolerated. Given that use of anabolic treatment is limited to 2 years, it should always be followed by antiresorptive treatment. Emerging research suggests a potential role of anabolic agents in the treatment of delayed fracture healing, although more randomized, placebo-controlled studies are needed.

Acknowledgments

Financial Support: This work was supported by the National Institutes of Health (Grant T32-HL-007609 to A.V.H.) and by grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health (Grants R01AR060574 and R01AR59775 to M.S.L.). The contents of this paper are solely the responsibility of the authors and do not necessarily represent the official view of the National Institute of Arthritis and Musculoskeletal and Skin Diseases or National Institutes of Health.

Correspondence: Andrea V. Haas, MD, Division of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, Massachusetts 02115. E-mail: ahaas2@bwh.harvard.edu.

Disclosure Summary: M.S.L. has equity ownership with Amgen and coauthorship of an abstract submission with Radius Health, Inc. A.V.H. has nothing to disclose.

References and Notes

1. Nguyen ND, Ahlborg HG, Center JR, Eisman JA, Nguyen TV. Residual lifetime risk of fractures in women and men. *J Bone Miner Res*. 2007;**22**(6):781–788.
2. Bliuc D, Alarkawi D, Nguyen TV, Eisman JA, Center JR. Risk of subsequent fractures and mortality in elderly women and men with fragility fractures with and without osteoporotic bone density: the Dubbo Osteoporosis Epidemiology Study. *J Bone Miner Res*. 2015;**30**(4):637–646.
3. Marrinan S, Pearce MS, Jiang XY, Waters S, Shanshal Y. Admission for osteoporotic pelvic fractures and predictors of length of hospital stay, mortality and loss of independence. *Age Ageing*. 2015;**44**(2): 258–261.
4. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. *Mayo Clin Proc*. 2008;**83**(9):1032–1045.
5. Dempster DW, Cosman F, Parisien M, Shen V, Lindsay R. Anabolic actions of parathyroid hormone on bone. *Endocr Rev*. 1993;**14**(6):690–709.
6. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med*. 2001;**344**(19):1434–1441.
7. Miller PD, Hattersley G, Riis BJ, Williams GC, Lau E, Russo LA, Alexandersen P, Zerbini CA, Hu MY, Harris AG, Fitzpatrick LA, Cosman F, Christiansen C; ACTIVE Study Investigators. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. *JAMA*. 2016;**316**(7):722–733.
8. Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, Maddox J, Fan M, Meisner PD, Grauer A. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med*. 2017;**377**(15):1417–1427.

9. 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): 141–149.
10. Wysolmerski JJ. Parathyroid hormone-related protein: an update. *J Clin Endocrinol Metab*. 2012; **97**(9):2947–2956.
11. Lippuner K, Zehnder HJ, Casez JP, Takkinen R, Jaeger P. PTH-related protein is released into the mother's bloodstream during lactation: evidence for beneficial effects on maternal calcium-phosphate metabolism. *J Bone Miner Res*. 1996;**11**(10):1394–1399.
12. Tella SH, Kommalapati A, Correa R. Profile of abaloparatide and its potential in the treatment of postmenopausal osteoporosis. *Cureus*. 2017;**9**(5):e1300.
13. Bahar H, Gallacher K, Downall J, Nelson CA, Shomali M, Hattersley G. Six weeks of daily abaloparatide treatment increased vertebral and femoral bone mineral density, microarchitecture and strength in ovariectomized osteopenic rats. *Calcif Tissue Int*. 2016;**99**(5):489–499.
14. Saag KG, Zanchetta JR, Devogelaer JP, Adler RA, Eastell R, See K, Krege JH, Krohn K, Warner MR. Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial. *Arthritis Rheum*. 2009;**60**(11):3346–3355.
15. Food and Drug Administration. TYMLOS (abaloparatide) injection. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2017/208743lbl.pdf. Accessed 23 January 2018.
16. Eli Lilly and Company. FORTEO teriparatide (rDNA origin) injection. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021318s015lbl.pdf. Accessed 23 January 2018.
17. Institute for Clinical and Economic Review. Anabolic Therapies for Osteoporosis in Postmenopausal Women: Effectiveness and Value. Boston, MA: ICER; 2017.
18. Vahle JL, Long GG, Sandusky G, Westmore M, Ma YL, Sato M. Bone neoplasms in F344 rats given teriparatide [rhPTH(1-34)] are dependent on duration of treatment and dose. *Toxicol Pathol*. 2004; **32**(4):426–438.
19. Jolette J, Wilker CE, Smith SY, Doyle N, Hardisty JF, Metcalfe AJ, Marriott TB, Fox J, Wells DS. Defining a noncarcinogenic dose of recombinant human parathyroid hormone 1-84 in a 2-year study in Fischer 344 rats. *Toxicol Pathol*. 2006;**34**(7):929–940.
20. Horwitz M, Stewart A, Greenspan SL. Sequential parathyroid hormone/alendronate therapy for osteoporosis–robbing Peter to pay Paul? *J Clin Endocrinol Metab*. 2000;**85**(6):2127–2128.
21. Orwoll ES, Scheele WH, Paul S, Adami S, Syversen U, Diez-Perez A, Kaufman JM, Clancy AD, Gaich GA. The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. *J Bone Miner Res*. 2003;**18**(1):9–17.
22. Leder BZ, O'Dea LS, Zanchetta JR, Kumar P, Banks K, McKay K, Lyttle CR, Hattersley G. 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.
23. Brunkow ME, Gardner JC, Van Ness J, Paeper BW, Kovacevich BR, Proll S, Skonier JE, Zhao L, Sabo PJ, Fu Y, Alisch RS, Gillett L, Colbert T, Tacconi P, Galas D, Hamersma H, Beighton P, Mulligan J. Bone dysplasia sclerosteosis results from loss of the SOST gene product, a novel cystine knot-containing protein. *Am J Hum Genet*. 2001;**68**(3):577–589.
24. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, Hofbauer LC, Lau E, Lewiecki EM, Miyauchi A, Zerbini CA, Milmont CE, Chen L, Maddox J, Meisner PD, Libanati C, Grauer A. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med*. 2016; **375**(16):1532–1543.
25. Gay A, Towler DA. Wnt signaling in cardiovascular disease: opportunities and challenges. *Curr Opin Lipidol*. 2017;**28**(5):387–396.
26. Langdahl BL, Libanati C, Crittenden DB, Bolognese MA, Brown JP, Daizadeh NS, Dokoupilova E, Engelke K, Finkelstein JS, Genant HK, Goemaere S, Hyldstrup L, Jodar-Gimeno E, Keaveny TM, Kendler D, Lakatos P, Maddox J, Malouf J, Massari FE, Molina JF, Ulla MR, Grauer A. 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):1585–1594.
27. Kendler DL, Marin F, Zerbini CAF, Russo LA, Greenspan SL, Zikan V, Bagur A, Malouf-Sierra J, Lakatos P, Fahrleitner-Pammer A, Lespessailles E, Minisola S, Body JJ, Geusens P, Möricke R, López-Romero P. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet*. 2018;**391**(10117):230–240.
28. Gold DT, Pantos BS, Masica DN, Misurski DA, Marcus R. Initial experience with teriparatide in the United States. *Curr Med Res Opin*. 2006;**22**(4):703–708.

29. Black DM, Greenspan SL, Ensrud KE, Palermo L, McGowan JA, Lang TF, Garnero P, Bouxsein ML, Bilezikian JP, Rosen CJ; PaTH Study Investigators. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *N Engl J Med*. 2003;**349**(13): 1207–1215.
30. Subbiah V, Madsen VS, Raymond AK, Benjamin RS, Ludwig JA. Of mice and men: divergent risks of teriparatide-induced osteosarcoma. *Osteoporos Int*. 2010;**21**(6):1041–1045.
31. Cipriani C, Irani D, Bilezikian JP. Safety of osteoanabolic therapy: a decade of experience [published correction appears in *J Bone Miner Res*. 2013;28(2):431]. *J Bone Miner Res*. 2012;**27**(12):2419–2428.
32. 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):1216–1226.
33. Cosman F, Eriksen EF, Recknor C, Miller PD, Guañabens N, Kasperk C, Papanastasiou P, Readie A, Rao H, Gasser JA, Bucci-Rechtweg C, Boonen S. Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1-34)] in postmenopausal osteoporosis. *J Bone Miner Res*. 2011;**26**(3): 503–511.
34. Lacey DL, Timms E, Tan HL, Kelley MJ, Dunstan CR, Burgess T, Elliott R, Colombero A, Elliott G, Scully S, Hsu H, Sullivan J, Hawkins N, Davy E, Capparelli C, Eli A, Qian YX, Kaufman S, Sarosi I, Shalhoub V, Senaldi G, Guo J, Delaney J, Boyle WJ. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. *Cell*. 1998;**93**(2):165–176.
35. Tsai JN, Uihlein AV, Lee H, Kumbhani R, Siwila-Sackman E, McKay EA, Burnett-Bowie SA, Neer RM, Leder BZ. Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. *Lancet*. 2013;**382**(9886):50–56.
36. 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):1838–1845.
37. Eastell R, Nickelsen T, Marin F, Barker C, Hadji P, Farrerons J, Audran M, Boonen S, Brixen K, Gomes JM, Obermayer-Pietsch B, Avramidis A, Sigurdsson G, Glüer CC. 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):726–736.
38. Black DM, Bilezikian JP, Ensrud KE, Greenspan SL, Palermo L, Hue T, Lang TF, McGowan JA, Rosen CJ; PaTH Study Investigators. One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis. *N Engl J Med*. 2005;**353**(6):555–565.
39. 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):992–997.
40. Lindsay R, Scheele WH, Neer R, Pohl G, Adami S, Mautalen C, Reginster JY, Stepan JJ, Myers SL, Mitlak BH. Sustained vertebral fracture risk reduction after withdrawal of teriparatide in postmenopausal women with osteoporosis. *Arch Intern Med*. 2004;**164**(18):2024–2030.
41. Leder BZ, Tsai JN, Uihlein AV, Wallace PM, Lee H, Neer RM, Burnett-Bowie SA. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. *Lancet*. 2015;**386**(9999):1147–1155.
42. Tsai JN, Nishiyama KK, Lin D, Yuan A, Lee H, Bouxsein ML, Leder BZ. Effects of denosumab and teriparatide transitions on bone microarchitecture and estimated strength: the DATA-Switch HR-pQCT study. *J Bone Miner Res*. 2017;**32**(10):2001–2009.
43. Cosman F, Miller PD, Williams GC, Hattersley G, Hu MY, Valter I, Fitzpatrick LA, Riis BJ, Christiansen C, Bilezikian JP, Black D. 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):200–210.
44. Andreassen TT, Ejersted C, Oxlund H. Intermittent parathyroid hormone (1-34) treatment increases callus formation and mechanical strength of healing rat fractures. *J Bone Miner Res*. 1999;**14**(6): 960–968.
45. Holzer G, Majeska RJ, Lundy MW, Hartke JR, Einhorn TA. Parathyroid hormone enhances fracture healing. A preliminary report. *Clin Orthop Relat Res*. 1999;**366**:258–263.
46. Andreassen TT, Willick GE, Morley P, Whitfield JF. Treatment with parathyroid hormone hPTH(1-34), hPTH(1-31), and monocyclic hPTH(1-31) enhances fracture strength and callus amount after withdrawal fracture strength and callus mechanical quality continue to increase. *Calcif Tissue Int*. 2004; **74**(4):351–356.
47. Komatsubara S, Mori S, Mashiba T, Nonaka K, Seki A, Akiyama T, Miyamoto K, Cao Y, Manabe T, Norimatsu H. Human parathyroid hormone (1-34) accelerates the fracture healing process of woven to lamellar bone replacement and new cortical shell formation in rat femora. *Bone*. 2005;**36**(4):678–687.

48. Almirol EA, Chi LY, Khurana B, Hurwitz S, Bluman EM, Chiodo C, Matzkin E, Baima J, LeBoff MS. Short-term effects of teriparatide versus placebo on bone biomarkers, structure, and fracture healing in women with lower-extremity stress fractures: A pilot study. *J Clin Transl Endocrinol*. 2016;**5**:7–14.
49. Aspenberg P, Genant HK, Johansson T, Nino AJ, See K, Krohn K, García-Hernández PA, Recknor CP, Einhorn TA, Dalsky GP, Mitlak BH, Fierlinger A, Lakshmanan MC. Teriparatide for acceleration of fracture repair in humans: a prospective, randomized, double-blind study of 102 postmenopausal women with distal radial fractures. *J Bone Miner Res*. 2010;**25**(2):404–414.
50. Johansson T. PTH 1-34 (teriparatide) may not improve healing in proximal humerus fractures. A randomized, controlled study of 40 patients. *Acta Orthop*. 2016;**87**(1):79–82.