Aging Clinical and Experimental Research (2021) 33:775–791
https://doi.org/10.1007/s40520-020-01708-8

REVIEW

# Role of bone-forming agents in the management of osteoporosis

**Michael R. McClung**[1,2]

Received: 18 July 2020 / Accepted: 1 September 2020 / Published online: 16 February 2021
© Springer Nature Switzerland AG 2021

**Abstract**
Recent evidence confirms the superiority of osteoanabolic therapy compared to anti-remodeling drugs for rapid improvement in bone density and fracture risk reduction, providing strong justification for the use of these anabolic agents as the initial therapy in high-risk patients, to be followed by anti-remodeling therapy. This review will highlight the results of recent studies and define the current status of osteoanabolic therapy for osteoporosis.

**Keywords** Osteoporosis · Osteoanabolic · Abaloparatide · Romosozumab · Teriparatide · Sequence

## Introduction

Osteoporosis affects at least half of postmenopausal women and perhaps 20% of older men [1]. It is a chronic disorder in which gradual, progressive bone loss after menopause in women and with aging in both men and women occurs because of an imbalance in the process of bone remodeling in which rates of bone resorption exceed that of bone formation. This causes deterioration of the architecture of both trabecular and cortical bone, weakening the skeleton and predisposing afflicted patients to experience fractures with even modest trauma.

The primary objective of medical management of patients with osteoporosis is to reduce the risk of fracture by improving bone mass and bone strength and by limiting the frequency of falls and injuries [2, 3]. While non-pharmacologic measures are important components of osteoporosis management, pharmacological intervention is required to effect significant skeletal strengthening. Most of the treatments available to treat osteoporosis are anti-remodeling drugs (often referred to an anti-resorptive agents), including the most commonly used medications, bisphosphonates, and denosumab. By decreasing the activity and/or number of bone-resorbing osteoclasts, these agents reduce the number and depth of resorption cavities, increase bone mineral density (BMD), strengthen the skeleton, and reduce fracture risk. However, they also indirectly reduce bone formation, precluding their ability to restore skeletal architecture toward or to normal.

Osteoanabolic action is necessary to stimulate new bone formation and to restore the damaged and disconnected trabecular architecture. Three biological drugs possessing osteoanabolic actions are now available for clinical use: teriparatide which has been in use since 2002 and two agents, abaloparatide and romosozumab, which have recently become available. (Table 1) While it seems intuitive that inducing greater increases in BMD and strengthening architecture with a bone-building agent should be more effective than anti-remodeling drugs, evidence to support that intuition has only recently become available [4, 5]. As a result, teriparatide has been used less often than less expensive and more convenient anti-remodeling drugs.

Recently, separate but related lines of evidence have provided new perspectives on the role of anabolic agents in the osteoporosis treatment paradigm. The strong relationship between BMD and fracture risk in untreated patients has been known for many years [6]. Studies with denosumab, romosozumab, and alendronate, drugs with very different mechanisms of action, have shown a significant relationship between on-treatment BMD achieved at the proximal femur and a patient's current risk of non-vertebral fracture [7, 8]. These studies were the first to document such a relationship while patients were receiving osteoporosis therapy. This important information was corroborated by a recent meta-regression analysis of 38 studies evaluating the effectiveness of 19 different drugs with varied effects on bone remodeling

✉ Michael R. McClung
mmcclung.ooc@gmail.com

[1] Oregon Osteoporosis Center, Portland, OR, USA

[2] Mary MacKillop Center for Health Research, Australian Catholic University, Melbourne, VIC, Australia

**Table 1** Osteoanabolic agents

| Drug | Mechanism of action | Effect on bone formation | Effect on bone resorption | Approved clinical dose | Route of administration |
|---|---|---|---|---|---|
| Teriparatide | PTH receptor agonist | Increased +++ Primarily remodeling based | Increased ++ | 20 ugm daily | SQ |
| Abaloparatide | Selective PTH receptor agonist | Increased ++ | Increased + | 80 ugm daily | SQ |
| Romosozumab | Humanized IgG2 anti-sclerostin antibody | Increased ++++, transient; primarily modeling based | Decreased | 210 mg QM | SQ |

*PTH* parathyroid hormone, *QM* once monthly, *SQ* subcutaneous

[9]. That study, funded by the Foundation of the National Institutes of Health, demonstrated strong and significant relationships between the magnitude of the increases in hip or spine BMD with osteoporosis therapies and the reduction in risks of vertebral, non-vertebral and hip fractures.

A second line of new information is a set of head-to-head clinical trials documenting the superiority of osteoanabolic agents over anti-remodeling agents for reducing fracture risk. These studies, discussed subsequently, provide the long-awaited justification for the proposition that therapy with a drug that rebuilds the skeleton should be the preferred treatment for osteoporosis, especially for patients at very high or imminent risk of fracture in whom rapid and substantial facture risk reduction is needed [10, 11].

Recent comprehensive reviews have provided in-depth analyses of each of the three anabolic agents [12–15]. This review will present the major clinical information of each of the three currently available bone-forming agents, including direct comparisons of these agents, on BMD and fracture risk with each other and with anti-remodeling drugs. Using this information, the newly defined roles of the osteoanabolic agents in the management of patents with osteoporosis will be discussed.

## Studies evaluating efficacy and safety including pivotal registration trials

### Teriparatide

Parathyroid hormone (PTH) is an 84 amino acid protein, secreted by the parathyroid glands, that modulates calcium metabolism by activating specific PTH1 receptors in bone and kidney [16, 17]. All of the known effects of PTH reside 9in the first 29 amino acids of the molecule. Teriparatide is a synthetic peptide consisting of the first 34 amino acids of intact human PTH (Table 1). Originally produced by laborious chemical peptide synthesis, it is now synthesized by recombinant DNA technology in bacteria.

Excessive levels of PTH, seen in patients with primary or secondary hyperparathyroidism, stimulate bone resorption and may be detrimental to the skeleton. While continuous administration of PTH is catabolic due to increased resorption, intermittent exposure is osteoanabolic, resulting in an overall improvement in bone balance [18]. By activating the surface-bound PTH1 receptor on osteoblasts and osteocytes, PTH induces the differentiation of stem cells and bone lining cells into functioning osteoblasts, enhances the activity of, and prolongs the lifespan of existing osteoblasts [19, 20]. PTH also reduces expression of sclerostin, an inhibitor of bone formation [21]. These actions, singly and in concert, increase the number and function of osteoblasts, increasing bone formation and mass. By stimulating secretion of receptor activator of nuclear factor kappa-β ligand (RANKL), PTH increases osteoclast activity and bone resorption [20].

#### Efficacy

The earliest clinical studies with teriparatide were conducted in publicly funded research laboratories. Daily subcutaneous (SQ) injection of teriparatide in doses of 25–100 ugm resulted in increased bone turnover, improved calcium balance in some by not all patients, and marked increases in bone formation and improved trabecular but not cortical volume on transiliac bone biopsies [22–24]. These results caused concern that the benefit of teriparatide on the trabecular compartment of the skeleton was occurring at the expense of the cortical compartment [22]. Estrogen was shown to blunt the acute rise in markers of bone resorption during teriparatide infusion in postmenopausal women [25]. This led to studies evaluating the effects of teriparatide combined with estrogen in women with postmenopausal osteoporosis and receiving glucocorticoid therapy, thinking that estrogen might protect the cortical skeleton from the induction by teriparatide of cortical porosity and bone loss [26, 27].

The Pivotal Fracture Trial (PFT), conducted by Eli Lilly and Company, evaluated the responses to daily SQ doses of 20 and 40 ugm of teriparatide in a high-risk cohort of 1637 women with postmenopausal osteoporosis and prior vertebral fracture [28] (Table 2). The trial, originally planned for 3 years, was abruptly truncated (average time from

**Table 2** Baseline characteristics of fracture end-point studies

| Study [reference] | Treatment group | Number of subjects | Age years (SD) | % with vertebral fractures at baseline | % with non-vertebral fractures at baseline |
|---|---|---|---|---|---|
| *Registration studies* | | | | | |
| Pivotal Fracture Trial [27] | Placebo | 448 | 69 (7) | 100% | NA |
| | Teriparatide | 444 | 69 (7) | 100% | NA |
| ACTIVE[32] | Placebo | 821 | 68.7 (6.5) | 22.9% | 32.4% |
| | Abaloparatide | 824 | 68.9 (6.5) | 21.5% | 30.1% |
| | Teriparatide | 818 | 68.8 (6.6) | 26.9% | 29.3% |
| FRAME [73] | Placebo | 3591 | 70.8 (6.9) | 18.0% | 21.8% |
| | Romosozumab | 3589 | 70.9 (7.0) | 18.7% | 21.7% |
| ARCH [75] | Alendronate QW | 2047 | 74.2 (7.5) | 95.9% | 37.6% |
| | Romosozumab | 2046 | 74.4 (7.5) | 96.2% | 37.5% |
| *Non-registration studies* | | | | | |
| Body 2002 [90] | Alendronate daily | 73 | 65 (9) | NA | NA |
| | Teriparatide | 73 | 66 (8) | NA | NA |
| Hadji 2012 [91] | Risedronate | 350 | 71.6 (8.1) | 90.0% | NA |
| | Teriparatide | 360 | 70.5 (8.8) | 89.7% | NA |
| VERO [95] | Risedronate | 680 | 71.6 (8.6) | 100% | 42% |
| | Teriparatide | 680 | 72.6 (8.8) | 100% | 44% |
| *In patients receiving glucocorticoids* | | | | | |
| Saag 2007 [92] | Alendronate daily | 214 | 57.3 (14.0) | 53 (25.4) | 89 (41.6) |
| | Teriparatide | 214 | 56.1 (4, 13) | 62 (30.0) | 93 (43.5) |

Study subjects were postmenopausal women except in Saag 2007 in which 19.4% of subjects were men

*NA* not available, *QW* once weekly, *SD* standard deviation

randomization to last study visit was 19 months) because of results of a rat carcinogenicity study (see below). BMD increased in the lumber spine by 9.7% with the 20 ugm dose and 13.7% with the higher dose. However, reductions in fracture risk, compared to placebo, did not differ between the two treatment groups, vertebral fracture relative risk 0.35 (95% CI 0.22, 0.55) with 20 ugm and 0.31 (0.19,0.50) with 40 ugm. Non-vertebral fracture risk was reduced by 35% and 40% with the 20 and 40 ugm doses, respectively.

When it was decided to proceed with filing for registration, study participants were recalled for additional evaluation. After a median of 6 months since leaving the original study, 1262 women enrolled in a follow-up study [29, 30]. Spine radiographs were obtained at an average of 18 months after treatment discontinuation. During that interval, the incidence of radiographic vertebral fractures was 41% lower in the group who had received 20 ugm teriparatide daily compared to the group who had received placebo ($p = 0.004$) [29]. Over a median of 30 months follow-up since treatment discontinuation, non-vertebral fracture risk was 36% lower in the combined teriparatide treatment groups compared to placebo ($p = 0.035$) [30]. These results were confounded by the fact that about 60% of the participants had received other osteoporosis medications (usually a bisphosphonate) during the 30-month follow-up study, but they did suggest a persistence of some of the protection from fracture for up to 30 months after stopping teriparatide therapy.

In an observational community-based study of women treated with teriparatide for 24 months, non-vertebral fracture risk was reduced by 36–51% in the latter three 6-month intervals compared to the first 6 months [31]. That risk reduction appeared to persist during a 24-month follow-up after discontinuing therapy.

Retreatment with teriparatide has been evaluated in small groups of patients with an interval of 12 months between courses of teriparatide during which patients received no therapy or a bisphosphonate [32–34]. Markers of bone formation and/or BMD increased with the second course of treatment, but the changes were somewhat less with the second course of therapy whether or not the patients had received a bisphosphonate [32, 33].

## Bone histology

Transiliac bone biopsies, obtained in 18 women who received teriparatide 20 ugm daily and 19 women who received placebo during the PFT, revealed no histological abnormalities, excess osteoid or woven bone [35]. Compared to placebo, teriparatide significantly increased cancellous bone volume and connectivity and cortical thickness.

An additional set of 23 transiliac biopsies were obtained after 12–18 months of treatment with teriparatide in the Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE) trial [36, 37]. No histological abnormalities were noted. Few significant differences were noted in histomorphometric indices compared to placebo. Cancellous bone volume was 19.8.% and 17.3% in the teriparatide and placebo groups, respectively. Mineral apposition rate and cortical porosity were increased with teriparatide. Stimulation of bone formation is more evident after shorter treatment intervals. After 3 months of teriparatide, large increases in bone formation were observed on cancellous, endocortical and periosteal surfaces [38]. Remodeling-based formation dominated on the former two surfaces. In a separate study, histomorphometric indices of bone formation were significantly increased after 6 months of therapy but returned to levels comparable with untreated postmenopausal women at 18 months [39]. This waning of the teriparatide anabolic effects may be due to increased Dkk1 levels, an inhibitor of bone formation [40].

## Safety

Teriparatide is generally well tolerated. Dizziness and syncope were more common with teriparatide than placebo in the PFT [28]. Orthostatic hypotension has been reported, especially with the first dose. Transient hypercalcemia was noted when serum calcium was tested 4–6 h after dosing in 11% of patients in the 20 ugm daily teriparatide group compared to 2% with placebo and 28% with teriparatide 40 ugm daily. Sustained hypercalcemia is uncommon. In the ACTIVE trial, hypercalcemia, based on albumin corrected serum calcium measured before and 4 h after injection, occurred in 0.4% of the placebo group and 6.4% with teriparatide [36]. Dose-dependent risk of bone tumors, including osteosarcoma, were observed when high doses of teriparatide were administered to a strain of rats predisposed to bone tumors [41]. A national surveillance registry has not detected a causal association between teriparatide treatment and osteosarcoma in humans [42].

## Registration

Teriparatide was first approved in the United States in 2002 for the treatment of women with postmenopausal osteoporosis and high risk of fracture. Registration in Europe and Australia occurred in 2003. The drug was subsequently approved to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture and to treat men and women with osteoporosis associated with chronic systemic glucocorticoid therapy. A boxed warning states that the drug should not be used in patients at increased risk for osteosarcoma, including patients with bone metastases or history of skeletal radiation. The drug should be used with caution in patients with a history of hypercalcemia or renal stones and in patients receiving digoxin. Transdermal and nasal preparations have been evaluated but are not registered for clinical use [43, 44].

In Japan, teriparatide is approved in a dose of 56.5 ugm administered SQ once weekly for 72 weeks. This approval was based upon a study documenting reduction in vertebral fracture risk from 14.5% with placebo to 3.1% with weekly teriparatide over an interval of 72 weeks (relative risk 0.20 (95% CI 0.09, 0.45) [45, 46]. Several teriparatide biosimilar preparations are available in Europe and parts of Asia and, recently, the first such product was approved by the FDA in the United States [47, 48].

## Dosing practicalities

Teriparatide is given as a daily SQ injection into the thigh or abdominal wall from a pre-filled syringe containing 28 doses [49]. Injections may be self-administered. The injection device should always be refrigerated. Patients should receive their first dose while sitting in case of dizziness or orthostatic hypotension. Since safety beyond 2 years was not assessed in the PFT, the cumulative use of any PTH analog for more than 2 years during a patient's lifetime is not recommended. No safety of laboratory monitoring is required except for serum calcium (measured 24 h after dosing) or urinary calcium in patients at risk for hypercalcemia or renal stones.

### PTH 1-84

The full-length active parathyroid hormone molecule (rhPTH 1–84), obtained by recombinant DNA technology, was evaluated in the Treatment of Osteoporosis study, an 18-month, randomized, placebo-controlled trial that enrolled 2532 postmenopausal women with osteoporosis [50]. Compared to placebo, PTH 1-84 100 ugm, administered daily by subcutaneous injection, reduced the incidence of a new vertebral fracture by 61%. No difference in non-vertebral fracture risk was observed. Hypercalcemia was reported in 27.8% of treated subjects vs 4.5% with placebo. PTH 1-84 did not receive approval from the US FDA, but it was approved in Europe in 2006. Because of low use by prescribers and without an American market, the marketing authorization for PTH 1-84 was withdrawn at the request of the marketing authorization holder [51].

### Abaloparatide

Abaloparatide is a synthetic 34 amino acid analog of parathyroid hormone-related peptide (PTHrP) that has 76% homology with human PTHrP 1-34 and 41% homology

with teriparatide [52] (Table 1). This specific molecule was selected by Radius Health from many candidate molecules to optimize the osteoanabolic effect relative to the anti-resorptive effect. Like teriparatide, abaloparatide stimulates bone formation by activating the PTH1 receptor on osteoblasts and osteocytes. In vitro, abaloparatide has a preferential selectivity for the RG conformation of the PTH receptor compared to teriparatide, resulting in a shorter duration of intracellular actions and less calcemic response with abaloparatide. In preclinical studies with ovariectomized rats and monkeys, abaloparatide increased trabecular and cortical BMD, microarchitecture, and bone strength with little or no increase in bone resorption [53–55].

## Efficacy

In a Phase 2 study, daily subcutaneous doses of 20, 40, and 80 ugm of abaloparatide were given to women with low bone mass and compared to open-label teriparatide 20 ugm daily [56]. Dose-dependent increases in BMD were observed over 24 weeks with abaloparatide. These results led to the daily dose of abaloparatide of 80 ugm being evaluated in the Phase 3 ACTIVE trial in which 2463 women (mean age, 69 years) were randomly assigned to receive abaloparatide, teriparatide 20 ugm daily, or placebo for 18 months [36] (Table 2). Larger increases were noted with abaloparatide than with teriparatide at 6 months. Compared to baseline, abaloparatide increased BMD in the lumbar spine by 10% and at the total hip by 4.1% at 18 months. New vertebral fractures and non-vertebral fractures were significantly reduced by 86% and 43%, respectively, with abaloparatide and by 80% and 28%, respectively, with teriparatide. The effects of the two drugs were not significantly different. Similar reductions in vertebral and non-vertebral risk were demonstrated with abaloparatide across subgroups defined by baseline age, BMD, prevalent fracture history, and renal function, according to geography and in patients with diabetes [57–60]. The incidence of wrist fracture was numerically reduced with abaloparatide therapy compared to placebo (HR 0.49, 95% CI 0.20,1.19, $p=0.11$) [61]. In a network meta-analysis of 10 pharmacological osteoporosis agents, abaloparatide reduced the relative risk of vertebral, non-vertebral, and wrist in postmenopausal women versus placebo compared with other treatment options [62].

In the ACTIVExtend Trial, 1139 of the 1243 eligible women who had completed the 18-month course of abaloparatide or placebo in the ACTIVE Trial were enrolled to receive open-label alendronate therapy for up to 24 months [63, 64]. BMD increased modestly in the group who transitioned from abaloparatide to alendronate, ultimately reaching an increase from the pre-treatment baseline of about 16% in the lumbar spine and about 6.3% in the total hip. While on alendronate for 24 months, vertebral fracture risk was 87% lower (0.37% vs. 2.82%) in the group who had received abaloparatide compared to the women who has received placebo. Non-vertebral, clinical, and major osteoporotic fracture risks were reduced by 39%, 34%, and 50%, respectively. Fracture risk reduction with the sequence of abaloparatide followed by alendronate was similar in subgroups of baseline age, BMD, and prevalent fracture status [65].

## Bone histology

A subset of women in the ACTIVE trial ($N=35$ placebo, 26 abaloparatide) underwent transiliac crest bone biopsies between 12 and 18 months of treatment [37]. No histological abnormalities, excess osteoid, or woven bone was noted. About 75% of the biopsy specimens were suitable for quantitative histomorphometry. Cancellous bone volume/total volume was 17.3% with placebo and 18.7% with abaloparatide. Eroded surface was lower and cortical porosity higher in the abaloparatide group.

## Safety

The overall incidence of adverse effects and serious adverse effects did not differ between abaloparatide and placebo in the ACTIVE study [36]. Nausea (8.3%), dizziness (10%), headache (7.5%), and palpitations (5.1%), generally mild to moderate in severity, occurred more frequently with abaloparatide than placebo. Hypercalcemia measured 4 h after injection occurred in 0.4% of the placebo group and 3.4% with abaloparatide. An association with bone tumors was observed in an abaloparatide rat toxicity study [41].

## Registration

Abaloparatide was approved in the United States in 2017 for the treatment of women with postmenopausal osteoporosis at high risk of fracture with the same boxed warning and the same restrictions regarding osteosarcoma as does teriparatide. Abaloparatide did not receive approval in Europe [66].

## Dosing practicalities

Abaloparatide is administered as a daily subcutaneous injection from a pre-filled syringe containing 30 doses [67]. Injections may be self-administered. The syringe should be refrigerated before its first use but can be kept at room temperature after it is opened. Patients should receive their first dose while sitting in case of dizziness or orthostatic hypotension. The cumulative use of either abaloparatide and/or teriparatide for more than 2 years during a patient's lifetime is not recommended. No safety or laboratory monitoring is required except in patients at risk for hypercalcemia or

renal stones. A microneedle transdermal patch formulation of abaloparatide is being developed [68].

### Romosozumab

Romosozumab is a humanized IgG2 monoclonal antibody with high specificity for human sclerostin, an osteocyte-derived glycoprotein that inhibits bone formation by binding to low-density lipoprotein receptor-related proteins 5 and 6, preventing activation of canonical Wnt signaling in bone [69] (Table 1). By inhibiting the skeletal effects of sclerostin, romosozumab increases bone formation while decreasing expression of RANKL and bone resorption. Bone formation is primarily modeling based, accounting for the large and rapid increases in bone mass [70]. In ovariectomized rats and gonad-intact female cynomolgus monkeys, anti-sclerostin therapy induced anabolic responses on all bone surfaces, increasing trabecular and cortical thickness, reducing cortical porosity, and substantially increasing bone mass and strength [71, 72].

In single- and multiple-dose phase 1 studies, divergent effects on biochemical indices of bone formation (increased) accompanied by a decrease in markers of bone resorption were observed [73, 74]. These effects on bone remodeling are very distinct from the reductions in both resorption and formation by anti-remodeling agents and the increases in both components of the remodeling cycle seen with teriparatide [36, 75].

## Efficacy

In an international phase 2 dose-finding study, 419 postmenopausal women with low bone mass were randomly assigned to receive various doses of romosozumab or placebo injections [14]. Dose-dependent increases in BMD were noted over 12 months of therapy, with changes from baseline being 11.3% in the lumbar spine and 4.1% in the total hip with the 210 mg once monthly (QM) dose of romosozumab, the highest dose evaluated. During the second year of therapy, additional increases of 3.8% and 1.3% in lumbar spine and total hip BMD, respectively, occurred [76]. Large increases in bone formation markers were observed after the first dose of romosozumab, but the post-dose increments gradually diminished over the course of the first year of therapy and post-dose values remained below baseline during year 2 of therapy. Bone resorption markers remained below baseline during the two-year study. Similar findings were observed in Japanese women with low bone mass [77]. Mechanisms for the waning of the anabolic effects could include upregulation of other inhibitors of bone formation or exhaustion of osteoblast precursors [78, 79]. Discontinuation of romosozumab resulted in return of BMD toward baseline over 12 months, whereas transitioning to denosumab after 2 years was associated with further gains in BMD [76]. These findings shaped the design of the Phase 3 fracture studies in which romosozumab was given for only 12 months followed by an anti-remodeling drug.

Retreatment with romosozumab for 12 months after 1 year of placebo or denosumab therapy was evaluated in the Phase 2 study extension [80]. The bone loss experienced while on placebo was promptly restored. In patients who received 2 years of romosozumab followed by 12 months of denosumab, lumbar spine BMD increased modestly (2.3%), hip BMD was maintained with retreatment, and the rebound in markers of bone remodeling expected upon discontinuation of denosumab was not observed.

In the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) a multi-national, randomized, double-blind placebo-controlled study, 7180 women at modest fracture risk were randomly assigned to placebo or romosozumab 210 mg QM for 12 months [81] (Table 2). Both groups then received open-label denosumab 60 mg Q6M for an additional 24 months [82]. Compared to placebo, romosozumab reduced the incidence of new vertebral fractures by 73% during the first 12 months of the study. During the second and third years of the study, while all women were receiving denosumab, the fracture protecting benefit of romosozumab persisted [81, 82]. During the first year of open-label denosumab therapy, 80% fewer women ($n=5$) who had received romosozumab had vertebral fractures than in the group who had taken placebo ($n=25$). The risk of clinical fractures (symptomatic vertebral fractures and non-vertebral fractures) was reduced by 36% compared to placebo at 12 months. No reduction in non-vertebral fracture risk was observed at 12 months (adjusted $p=0.10$). In a prespecified subgroup analysis, the incidence of non-vertebral fractures in the 43% of the study population from Latin America was noted to be particularly low (1.2% in the placebo group over 12 months). In a post hoc analysis, non-vertebral fracture risk was significantly reduced after 12 months of therapy by 42% in all study sites after excluding those from Latin America. We should recall that non-vertebral fracture risk reduction at 12 months has rarely been observed with any osteoporosis treatment. Analyses of subgroups defined by baseline age, BMD, and fracture status were consistent with the overall study results.

The Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) was the first active-controlled registration study in our field. A total of 4093 women with postmenopausal and high fracture risk (almost all had a previous fracture) were randomized to receive romosozumab 210 mg QM or oral alendronate 70 mg QW for 12 months, followed by open-label alendronate therapy in both treatment groups for up to an additional 2 years [83]. (Table 2) At 12 months, a relative reduction in vertebral fracture risk of 37% was seen with romosozumab

vs. alendronate. Vertebral fracture risk was 48% lower at 24 months in the women who had taken romosozumab for the first 12 months compared to the group who received alendronate during year 1 (6.2% vs. 11.9%), demonstrating again that the vertebral fracture benefit afforded by the anabolic therapy persisted after transitioning to an anti-remodeling agent. The 26% reduction in non-vertebral fracture risk with romosozumab at 12 months was not quite statistically significant. However, at the primary analysis (median of 2.7 years in this event-driven trial), non-vertebral fracture risk was reduced by 19% ($p = 0.037$), clinical fracture risk was reduced by 28% ($p \leq 0.001$) and hip fracture risk by 38% ($p = 0.015$) in the romosozumab group compared to the alendronate group. BMD changes were much greater at 12 months with romosozumab compared to alendronate (Table 4), and this difference remained for the duration of the study.

## Bone histology

A subset of 107 women in the FRAME study underwent transiliac bone biopsy at month 2 or month 12. At month 2, significant increases in indices of formation and decreases in bone resorption parameters were noted with romosozumab [84]. At month 12, evidence of increased bone formation was no longer present, but the romosozumab group had increased bone mass and trabecular thickness, improved trabecular connectivity, and no increase in cortical porosity.

## Safety

The overall incidence of adverse and serious adverse events (SAEs) in FRAME and ARCH did not differ between romosozumab and control groups [81, 83]. Mild injection site reactions were reported in 4.4–5.2% of participants receiving romosozumab vs. 2.6–2.9% of controls. Mild reductions in serum calcium have been reported [81, 83, 85]. Single adjudicated cases consistent with osteonecrosis of the jaw and femoral shaft fracture with atypical findings were observed during the year of romosozumab therapy in FRAME [81]. Hypersensitivity reactions have been reported infrequently. Anti-romosozumab antibodies have been detected in 15–20% of patients during the first year of therapy, including rare patients with neutralizing antibodies. However, these antibodies were not associated with altered efficacy, injection site reactions, hypersensitivity, or other adverse events.

Canonical Wnt signaling modulates cellular growth, including neoplasms. No differences in rates of malignancy between romosozumab groups and control groups in FRAME and ARCH studies, and no treatment-related effects on tumor incidence, including bone tumors, were observed in a lifetime study in rats treated with romosozumab [86].

Because sclerostin is expressed in small amounts in vascular smooth muscle tissue, a formal adjudication process was established to review and adjudicate all cardiovascular (CV) SAEs in the FRAME and ARCH studies. The adjudicating committee of expert cardiologists also performed a post hoc analysis comparing rates of major adverse cardiac events (MACE) consisting of non-fatal stroke and MI and CV deaths. In FRAME over 12 months, CV SAEs occurred in 1.5% of both romosozumab and placebo treatment groups, and MACE was observed in 0.8% of each group [81, 87]. However, after 12 months of therapy in ARCH, adjudicated CV SAEs occurred more often with romosozumab (2.5%) than alendronate (1.9%; odds ratio, 1.31; 95% CI, 0.85 to 2.00) [83]. MACE occurred in 41 subjects (2.0%) with romosozumab and 21 (1.1%) with alendronate, resulting in a hazard ratio of 1.87 (95% CI 1.11,3.14) In contrast to the differences in ischemic CV events, the incidences of heart failure, non-coronary revascularization, and peripheral vascular ischemic events not requiring revascularization were numerically lower in the romosozumab group [83]. The difference in ischemic CV event between the two treatment groups occurred during the first few months in the ARCH study and did not progress with longer-term treatment or upon transition to alendronate, and subgroup analyses did not identify a subset of patients who were particularly susceptible to the observed CV risks [87]. Thirty of the 2040 women (1.5%) in the romosozumab group died during the first year of ARCH compared to 21 of 2014 (1.0%) women taking alendronate.

The reason(s) for the disparity in CV safety results from the FRAME and ARCH studies is not known. Although sclerostin has been hypothesized to inhibit progression of atherosclerosis, no CV signal was noted in preclinical studies in sclerostin-deficient animals or with anti-sclerostin therapy [87, 88]. While some studies have demonstrated cardioprotection and reduced mortality with intravenous bisphosphonate therapy, meta-analyses have not identified a relationship between oral bisphosphonate therapy and CV risk [89–92]. The possibility that the difference in CV events in the ARCH study is simply due to chance has been suggested [93, 94].

In the FRAME study, 23 (0.6%) of women died during the 12 months of placebo therapy compared to 29 (0.8%) in the romosozumab group [81]. In the ARCH study, where the average age was 74 years, 4 years older than the mean age in FRAME, all-cause mortality was 1.0% in the alendronate group and 1.5% in the romosozumab group during the first 12 months of the study [83]. However, mortality was significantly greater with romosozumab (2.0% vs 1.2%; HR 1.71, 95% CI 1.06–2.78) in the subgroup of women aged 75 and older [95].

### Registration

Romosozumab was registered in Japan and the United States in early 2019 for the treatment of women with postmenopausal osteoporosis and high risk of fracture. The drug has subsequently been registered in Europe and many other countries. The drug is marketed by UCB and Amgen who collaborated on the clinical development of the drug since 2004. Therapy is approved for an interval of 12 months to be followed by an anti-remodeling agent. There is no limit on lifetime exposure. The CV safety data in the ARCH study resulted in warnings in the romosozumab prescribing information in Europe, the United States, and other countries [95, 96]. The use of romosozumab is contraindicated in patients with a history of myocardial infarction or stroke within the preceding year. For other patients the benefit of fracture reduction should be weighed against the risk of CV events, and romosozumab should only be used if the benefit outweighs the risk. Therapy should be discontinued if a patient experiences a stroke or heart attack while taking romosozumab.

### Dosing practicalities

Romosozumab is given as two subcutaneous injections, each in a single-use, pre-filled syringe containing 105 mg of the drug, into abdomen, thigh, or upper arm once monthly for 12 doses [96]. The injections are to be administered by a health care provider. Hypocalcemia and hypersensitivity to the drug are contraindications. There is no contraindication for use in patients with impaired renal function, cancer, or risk factors for osteosarcoma.

## Ancillary clinical information

### Adherence to anabolic therapies

Efficacy of any therapy requires adherence to the treatment regimen. Even short-term persistence to oral bisphosphonate therapy is poor with most patients discontinuing their drug within the first year of treatment [97]. Substantial heterogeneity exists in reports of adherence rates with teriparatide with results ranging from 21 to 89% at 1 year (median 53%) and 37 to 68% (median 40%) at 2 years [98]. Adherence to abaloparatide and romosozumab has not yet been evaluated.

### Head-to-head comparison studies

Comparing the effects of osteoporosis treatments across studies is problematic because of differences in assessments, baseline characteristics, and fracture risk in the study cohorts (Table 2). A much clearer sense of relative efficacy and safety can be derived from head-to-head comparisons when study participants are randomly assigned to treatment groups.

### Comparisons with anti-remodeling drugs

In addition to the ARCH study, several studies have directly compared anabolic agents to other osteoporosis treatments. Most of those studies compared changes in BMD as detailed in Table 3. Such comparisons are thought to have significance because of the aforementioned associations between treatment-associated BMD changes and fracture risk [9]. In direct comparisons, teriparatide or abaloparatide treatment resulted in consistently larger increases in BMD at the spine and proximal femur than did oral bisphosphonates [56, 75, 99–101]. Larger increases in lumbar spine BMD but smaller BMD gains at the total hip were seen with teriparatide compared to zoledronate or denosumab [102, 103]. Romosozumab was associated with larger BMD gains than alendronate [83, 85].

Fewer studies have directly compared fracture risk reduction (Table 4). The superior fracture risk reduction of romosozumab over alendronate in the ARCH trial has been discussed [36, 83]. Three studies have demonstrated greater reduction in vertebral fracture risk with teriparatide than with an oral bisphosphonate in women with postmenopausal osteoporosis or patients receiving glucocorticoid therapy [100, 101, 104]. The VERO trial is of particular importance because of its size (1360 participants), duration of therapy (24 months), and that most patients had previously received bisphosphonate therapy [104]. In that study of postmenopausal women with prior vertebral fractures, vertebral fracture risk was reduced with teriparatide compared to risedronate by 48% (RR 0.52; 95% CI 0.30, 0.91) at 12 months and by 56% (RR 0·44; 95% CI 0.29, 0.68) at 48 months. Clinical fracture risk was reduced by 52% at 24 months ($p = 0{\cdot}0009$) but the 34% in non-vertebral fracture risk was not statistically significant. A smaller study demonstrated a 70% greater reduction in non-vertebral fracture risk with teriparatide compared to alendronate after 12 months treatment [99]. These head-to-head study results showing greater effects on BMD and fracture risk reduction with an anabolic agent compared to either a bisphosphonate or to denosumab are supported by the final results of the ACTIVExtend and FRAME studies [64, 81, 82]. Lower fracture risk was observed in patients receiving anti-remodeling agents for up to 2 years who had been pretreated with an anabolic drug for 12–18 months compared to pretreatment with placebo. Collectively, these studies clearly document the superiority of an anabolic agent compared to either an oral bisphosphonate or to denosumab for rapid increase in BMD and reduction in fracture risk.

**Table 3** Head-to-head comparisons of BMD responses to anabolic drugs vs. other agents

| Study [reference] | Treatment group | Number of subjects | Therapy (months) | BMD % (±SE) or (95% CI)* | | |
|---|---|---|---|---|---|---|
| | | | | Lumbar spine | Total hip | Distal (1/3) radius) |
| Body 2002 [90] | Alendronate daily | 73 | 12 | 6%** | 2.2%** | |
| | Teriparatide | 73 | | 14%** | 4.9%** | |
| FACT-Lilly [68] | Alendronate daily | 101 | 18 | 5.5% | 3.5%*** | |
| | Teriparatide | 102 | | 10.3% | 3.9%*** | |
| Hadji [91] | Risedronate | 350 | 18 | 2.6 ± 0.5% | 0.83 ± 0.5% | |
| | Teriparatide | 360 | | 7.8 ± 0.5% | 2.05 ± 0.4% | |
| Cosman [93] | Zoledronate | 137 | 12 | 4.4% | 2.2% | |
| | Teriparatide | 138 | | 7.0% | 1.1% | |
| DATA [94] | Denosumab | 33 | 24 | 8.3% ± 3.4 | 3.2% ± 2.5 | 2.1% ± 3.1 |
| | Teriparatide | 31 | | 9.5% ± 5.9 | 2.0% ± 3.0 | − 1.7% ± 4.6 |
| Abaloparatide Phase 2 [50] | Placebo | 45 | 6 | 1.6 ± 3.4% | 0.4 ± 3.1% | |
| | Abaloparatide | 45 | | 6.7 ± 4.2% | 2.6 ± 3.5% | |
| | Teriparatide | 45 | | 5.5 ± 4.1% | 0.5 ± 3.9% | |
| ACTIVE [32] | Placebo | 821 | 18 | 0.6% | − 0.1% | − 0.6% |
| | Abaloparatide | 824 | | 11.2% | 4.2% | − 1.0% |
| | Teriparatide | 818 | | 10.5% (10.1, 10.9) | 3.3% (3.0, 3.5) | − 2.3% |
| Romosozumab Phase 2 [77] | Placebo | 52 | 12 | − 0.1% (− 1.2 to 0.9) | − 0.7 (− 1.4, − 0.1) | − 0.9 (− 1.8, 0.1) |
| | Romosozumab | 52 | | 11.3 (10.3, 12.4) | 4.1 (3.5, 4.8) | − 1.2 (− 2.1, − 0.2) |
| | Alendronate QW | 51 | | 4.1 (3.0, 5.1) | 1.9 (1.3, 2.6) | − 0.3 (− 1.2, 0.7) |
| | Teriparatide | 55 | | 7.1 (6.1, 8.2) | 1.3 (0.7, 2.0) | − 1.7 (− 2.7, − 0.7) |
| ARCH [75] | Alendronate QW | 1757–1829 | 12 | 5.0% | 2.8% | |
| | Romosozumab | 1750–1826 | | 13.7% | 6.2% | |
| STRUCTURE [99] | Teriparatide | 209 | 12 | 5.4% | − 0.5% (− 1.0, − 0·2) | |
| | Romosozumab | 206 | | 9.8% | 2.6% (2.2, 3.0) | |
| *In GIOP* | | | | | | |
| Saag 2007 [92] | Alendronate daily | 214 | 18 | 3.4 ± 0.7% | 2.4 ± 0.6% | |
| | Teriparatide | 214 | | 7.2 ± 0.7%. | 3.8 ± 0.6% | |

*CI* confidence interval, *QW* once weekly, *SE* standard error

*SE or 95% CI provided when available

**Estimated from Figs. 1 and 2 in Body [99]

***Femoral neck BMD listed since total hip BMD was not available

## Comparisons of anabolic agents with each other

In direct comparisons, BMD responses were greater with abaloparatide 80 ugm daily than with teriparatide 20 ugm daily [56, 105] (Table 3). Compared to placebo, the relative risk reductions in vertebral, non-vertebral and clinical fractures were numerically lower with teriparatide compared to abaloparatide but the differences between the two active treatments were not statistically significant [36] (Table 4). The reduction in major osteoporotic fracture, a pre-specified exploratory endpoint, was greater with abaloparatide than with teriparatide (HR 0.45; 95% CI 0.21, 0.95; $p = 0.30$) [36]. The overall incidence of AEs and SAEs did not differ between abaloparatide and teriparatide in the ACTIVE study. Hypercalcemia occurred more often with teriparatide (6.4%) than with abaloparatide (3.4%).

Teriparatide and romosozumab have been compared in two studies. In the romosozumab Phase 2 study, BMD increased more over 12 months with romosozumab than teriparatide at the lumbar spine and total hip [85] (Table 3). Volumetric BMD of the spine and especially the hip was greater with romosozumab than with teriparatide as were finite element analysis (FEA) estimates of bone strength [106, 107]. In a study of 436 women with osteoporosis previously treated with bisphosphonates for at least 3 years (mean = 6 years), areal and volumetric BMD of the lumbar spine and proximal femur increased more with romosozumab than with teriparatide as did estimates of bone strength by FEA [108]. Adverse events were similar between treatment groups except that transient hypercalcemia occurred more commonly with teriparatide (10% vs. < 1%).

**Table 4** Head-to-head comparisons of fracture risk with anabolic drugs vs. other agents

| Study [reference] | Treatment group | Therapy (Months) | Vertebral fracture % | Relative risk (95% CI) | Non-vertebral fracture % | Hazard ratio (95% CI) |
|---|---|---|---|---|---|---|
| Body 2002 [90] | Alendronate daily | 12 | NA | | 13.7% | |
| | Teriparatide | | NA | | 4.1% | RR 0.30<br>$p=0.042$ |
| Hadji [91] | Risedronate | 18 | 9.4% | | 8.3% | |
| | Teriparatide | | 4.4% | 0.53<br>$p=0.01$ | 7.8% | RR 0.06<br>p=0.89 |
| VERO [95] | Risedronate | 24 | 12.0% | | 6.1% | |
| | Teriparatide | | 5.4% | 0·44 (0.29,0.68) | 4.0% | 0.66 (0.39,1.10) |
| ACTIVE [32] | Placebo | | 4.2% | | 4.7% | |
| | Abaloparatide | 18 | 0.6% | vs. placebo 0.14 (0.05,0.39) | 2.7% | vs. placebo 0.57 (0.32,1.00) |
| | Teriparatide | | 0.8% | vs. placebo 0.20 (0.08,0.47) | 3.3% | vs. placebo 0.72 (0.42,1.22) |
| Arch [75] | Alendronate QW | 12 | 6.3% | | 4.6% | |
| | Romosozumab | | 4.0% | 0.63 (0.47,0.85) | 3.4% | 0.74 (0.54,1.01) |
| *In glucocorticoid-induced osteoporosis* | | | | | | |
| Saag 2007 [92] | Alendronate daily | | 6.1% | | 3.7% | 0.36 |
| | Teriparatide | 18 | 0.6% | 0.004 | 5.6% | |

*CI* confidence interval, *QW* once weekly, *RR* relative risk

## Sequential use of osteoporosis drugs

Caring for patients with osteoporosis requires having a lifelong management plan, taking advantage of all treatment options. Although we are still searching for the optimal treatment strategy, it is now very apparent that using an osteoanabolic treatment followed by an anti-remodeling drug results in greater gains in BMD that occurs when the reverse sequence is used. However, since many patients are treated initially with an anti-remodeling drug, evidence regarding the use of anabolic agents following those therapies will be reviewed.

## Anabolic agents followed by anti-remodeling drugs

Teriparatide and romosozumab treatment should be followed by an anti-remodeling drug to prevent the rapid loss in BMD that occurs when treatment is stopped. While studies have not evaluated the BMD response to discontinuing abaloparatide, it is likely to mimic the effect of stopping teriparatide. Bisphosphonates and denosumab, the drugs most often used as follow-on therapy, effectively preserve or increase BMD when anabolic therapies are stopped [64, 76, 81, 83, 109, 110]. The results of the ACTIVExtend, FRAME, and ARCH studies also make it clear that the fracture protection realized from 12 to 18 months of treatment with an anabolic drug persist for at least 2 years after patients transition to alendronate or denosumab [64, 83, 111]. Raloxifene, a weak anti-remodeling agent, given after a 12-month course of teriparatide, blunted or prevented bone loss in the lumber spine and increased proximal femur BMD [112, 113].

## Anabolic agents after anti-remodeling drugs

Smaller gains in BMD (or even decreases in cortical BMD), especially in the first 6–12 months, are achieved when teriparatide is used following bisphosphonate treatment than in treatment-naïve patients [114–118]. This is a predictable result since the BMD increase with all osteoporosis drugs is directly related to the rate of bone turnover when treatment is started [119–121]. The decline in cortical BMD with teriparatide after bisphosphonate therapy is accompanied by an increase in cortical thickness and porosity and no change in estimated hip bone strength [118, 122]. In a European study, 29 postmenopausal women were switched to teriparatide 20 µg daily after having taken alendronate for at least 33 months. Lumbar spine and femoral neck BMD increased by 5.3% and 3.3%, respectively, after 24 months of teriparatide compared to increases of 10.2% in the spine and 5% in the femoral neck in 16 matched treatment-naïve patients [116]. However, biochemical and histological indices of bone formation as well as measures of bone structure were similar in the groups who had and had not received prior bisphosphonate therapy [123–125]. Smaller BMD responses to both teriparatide and romosozumab were also noted in women who had taken bisphosphonates for at least 3 years than observed in other studies without previous bisphosphonate exposure [108].

These results suggest that stimulation of bone formation and increased BMD with anabolic therapies may be somewhat delayed in patients with vs. without previous bisphosphonate exposure but are still robust. How these smaller and slower responses to osteoanabolics after bisphosphonates

relate to fracture risk reduction is unclear. In the VERO trial, 59% of the subjects in the teriparatide group had previously received bisphosphonates, and the effect of teriparatide on fracture risk reduction, compared to risedronate, was evident [104].

Transition from 2 years of denosumab to teriparatide resulted in transient decreases in both lumbar spine and, especially, proximal femur BMD [109]. This result likely reflects the inability of teriparatide to prevent the rebound in bone remodeling that occurs when denosumab in discontinued [126]. One year of romosozumab treatment following 12 months of denosumab prevented the expected rebound in remodeling and preserved or slightly increased BMD [80].

## Combining anabolic and anti-remodeling agents

The concept of combining a PTH receptor agonist with an anti-remodeling drug to inhibit the increase in bone resorption began many years ago with the simultaneous use of teriparatide or PTH 1-84 and estrogen [26, 27, 127]. Large increases in BMD were observed, demonstrating a robust osteoanabolic response to the PTH analog, but none of those studies compared the effects of that combination with teriparatide monotherapy. A 6-month study did compare teriparatide plus raloxifene with teriparatide alone in women with postmenopausal osteoporosis [128]. The addition of raloxifene did not reduce bone formation, as assessed by serum P1NP, and the increase in bone resorption due to teriparatide was attenuated but not prevented. BMD increases were greater with combined therapy vs. teriparatide alone, and the difference at the hip was statistically significant. Adding teriparatide to ongoing raloxifene therapy resulted in no BMD advantage after 18 months of therapy compared to switching from teriparatide to raloxifene [117].

Combining PTH receptor agonists, including PTH 1-84, with a bisphosphonate has resulted in variable BMD responses compared to PTH analog monotherapy [5]. The most important of these studies was the simultaneous initiation of teriparatide with an intravenous infusion of zoledronate compared to teriparatide and zoledronate monotherapies [102]. At 13 and 26 weeks, BMD increases were greater at the lumbar spine and total hip with combined therapy, but by 52 weeks, the differences between the combined therapy group and zoledronate monotherapy were no longer apparent.

The most interesting combination therapy regimen is that of teriparatide with denosumab because the increase in bone resorption with teriparatide is due to upregulation of RANKL. This combination was evaluated a cohort of 94 postmenopausal women with osteoporosis randomized to take teriparatide, denosumab, or both [129]. Bone resorption was dominated by denosumab, while bone formation decreased more slowly in the combination group than in the denosumab group. Lumbar spine and hip BMD increased more with combined therapy than with either monotherapy. That BMD advantage of combined therapy persisted but did not become larger during the second year of the study [103]. Combined therapy was superior to teriparatide but not denosumab in most parameters of bone structure and to both monotherapies in bone strength estimated by FEA of the radius and tibia after 12 months of treatment [130] These advantages of combined over single drug treatment were less evident after 24 months [131]. Similar BMD and bone turnover marker findings were observed in an even smaller Japanese study comparing the combination of denosumab plus teriparatide with denosumab alone over 24 months [132]. There was not a teriparatide comparison group. These differences persisted over a 48-month treatment interval [133]. Significantly larger increases in BMD were observed over 15 months with the combination of teriparatide 40 ugm daily plus denosumab compared to the approved 20 ugm dose of teriparatide [134]. Whether these BMD effects of combined therapy result in faster or greater reductions in fracture risk is unclear.

In a unique study design, teriparatide was added 3 months after denosumab therapy was begun [135]. Changes in BMD were numerically but not significantly greater in the combination therapy group compared to single therapy. Unlike the studies in which teriparatide and denosumab were begun simultaneously, average serum CTX values returned to baseline and serum P1NP rose to levels above baseline in the combination therapy group at 12 months, providing a favorable balance between bone formation and resorption.

A meta-analysis evaluated the effects of teriparatide combined with anti-remodeling therapies vs. monotherapy in 19 randomized clinical trials [136]. Combination therapy, driven primarily by the studies evaluating the combination of teriparatide and denosumab, was superior to monotherapy regarding improvement of the lumbar spine and total hip BMD, without risk of serious adverse events. Combination therapy also appeared to have an advantage over monotherapy on fracture risk reduction although the confidence in that outcome was limited by the paucity of fracture data in these studies. Combinations with either abaloparatide or romosozumab have not been evaluated.

## Cost-effectiveness

Decisions about using specific osteoporosis drugs are often based upon health economic considerations. Such analyses depend upon several factors and assumptions beyond simple cost and effectiveness such as the fracture risk in the target population, comorbid conditions, and estimated adherence to therapy. For anabolic drugs administered for only 12–24 months, the follow-on treatment and its duration are also important variables. Even estimates of efficacy can

be problematic when data from separate studies are used to compare absolute reduction in risk.

In the United States the differences in medication cost is great between branded anabolic agents and generic anti-remodeling drugs. As a result, economic analyses do not support the use of any of the anabolic drugs compared to low-cost alternatives [137–139]. One analysis demonstrated that teriparatide reduced fractures more effectively than did alendronate but that the incremental cost of teriparatide over generic alendronate was $455,000 and $1,555,000 per vertebral and non-vertebral fracture prevented, respectively [137]. In the 2020 National Institute for Health Research report, both teriparatide and romosozumab were considered to be effective in preventing fractures, but the incremental cost-effectiveness ratios were greater than the commonly applied threshold of £20,000–30,000 per quality-adjusted life-year. [139] An exception was a study using health services data from the United States in very high-risk patients in which abaloparatide for 18 months followed by alendronate for 5 years was cost-effective compared to generic alendronate monotherapy [140]. This study had the advantage of the data from the ACTIVExtend study which precluded some of the difficulties in making comparisons across studies. Separate analyses using data from that study demonstrated that the sequence of abaloparatide therapy followed by alendronate for 5 years was cost-effective compared with treatment with teriparatide for 18 months followed by alendronate for 5 years in American women at high risk of fracture [141, 142]. The advantage of abaloparatide in these studies was driven primarily by difference in cost in the US market. To date, a cost-effective analysis based on the ARCH study head-to-head comparison of romosozumab followed by alendronate compared to alendronate monotherapy has not been generated.

## Osteoporosis in men

A study was conducted with 437 men having idiopathic or hypogonadal osteoporosis who were randomized to receive teriparatide therapy 20 ugm or 40 ugm daily or placebo [143]. As occurred in the teriparatide PFT, study participants were discharged early from the study after a median of 11 months of therapy when the rat osteosarcoma study results became available. During that interval of therapy, gains in BMD with teriparatide 20 ugm daily at the lumbar spine and total hip were 5.9% and 1.2%, respectively, from baseline compared to changes of 0.5% at both sites with placebo. About 6 months after the original study was discontinued, the study cohort was reconvened to be followed for an additional 24 months. Spine radiographs taken about 18 months after discontinuation of study medication demonstrated a 51% reduction of new vertebral fractures in the combined teriparatide groups compared to placebo (absolute risk reduction 6%; $p = 0.07$) [144]. There are no studies of abaloparatide in men.

Romosozumab was evaluated in 265 men with osteoporosis, randomized 2:1 to receive romosozumab 210 mg QM or placebo for 12 months. Increases at the lumbar spine (12.1% vs. 1.2%) and total hip (2.5% vs. −0.5%) were significantly greater with romosozumab than with placebo [145]. While the frequency of AEs and SAEs were similar between treatment groups, there was a numerical imbalance in the positively adjudicated CV SAEs [romosozumab 8 (4.9%); placebo 2 (2.5%)]. Only 5 clinical fractures were observed, precluding meaningful comparison between treatment groups.

## Glucocorticoid therapy

Because the pathogenesis of glucocorticoid-induced osteoporosis (GIOP) involves inhibition of bone formation, there is special interest in the roles of anabolic therapies in these patients. Teriparatide therapy, compared to alendronate, significantly increased BMD and reduced vertebral fracture risk, compared to alendronate, over 18 months in 428 men and women receiving glucocorticoid therapy [101]. (Tables 3, 4) No clinical studies with either abaloparatide or romosozumab have been conducted in GIOP. In rabbits, abaloparatide 25 µg/kg/day significantly increased trabecular and cortical BMD and femoral strength [146].

## Premenopausal women with low bone mass

Neither abaloparatide nor romosozumab has been studied in this population. Teriparatide therapy for 18–24 months increased BMD and improved cortical and trabecular architecture in a small number of women with premenopausal osteoporosis [147, 148]. Increases in BMD have also been observed with teriparatide therapy in women with osteoporosis associated with pregnancy and lactation [149]. Teriparatide is not approved for use in these patients.

## Fracture healing

Studies with all three anabolic agents have shown improved fracture healing in rodents and, with romosozumab, in subhuman primates [150–153]. Despite substantial enthusiasm among orthopedists for the use of anabolic drugs to promote fracture healing, there is limited clinical evidence to support this practice. The primary endpoint was not met in a formal study to evaluate healing of distal radius fractures with teriparatide [154]. However, in a post hoc analysis, time to fracture healing was significantly reduced from 9.1 to 7.4 weeks with teriparatide 20 ugm daily compared to placebo. Clinical studies with romosozumab have not shown accelerated healing after tibial or hip fractures [155, 156].

## Summary

Strong clinical evidence now exists that osteoanabolic agents increase bone mass and improve skeletal microstructure, leading to a stronger skeleton and more rapid and more effective protection from fractures than do antiremodeling therapies. Importantly, these benefits are then maintained for at least 2 years upon transitioning to antiremodeling therapy, extending the benefit of the bone-building therapy. Total hip BMD, a proven surrogate for fracture risk, increases more and faster with this treatment sequence than with any other treatment regimen. Because of cost considerations, the current roles of anabolic drugs include their use as primary therapy in very high-risk patients or, based on the VERO and STRUCTURE studies, in patients who remain at high fracture risk after a course of bisphosphonate therapy. If or when costs of the drugs become lower, these osteoanabolic therapies will be appropriate for all patients with osteoporosis in need of skeletal reconstruction and/or rapid reduction in fracture risk.

**Disclosures** Funding None reported.

### Compliance with ethical standards

**Conflicts of interest** The author states that he receives consulting fees from Amgen and Myovant and honorarium for speaking from Amgen.

**Statement of human and animal rights** For this review article, no novel, original human participant or animal studies were performed.

**Informed consent** For this review article, formal consent of participants was not required.

**Role of the author** The author personally performed the literature search and wrote the review paper.

## References

1. Compston JE, McClung MR, Leslie WD (2019) Osteoporosis. The Lancet 393:364–376
2. Kanis JA, Cooper C, Rizzoli R et al (2019) European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 30:3–44
3. Camacho PM, Petak SM, Binkley N et al (2020) American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the diagnosis and treatment of postmenopausal osteoporosis—2020 Update. Endocr Pract 26:1–46
4. Cosman F, Nieves JW, Dempster DW (2017) Treatment sequence matters: anabolic and antiresorptive therapy for osteoporosis. J Bone Miner Res 32:198–202
5. McClung MR (2017) Using osteoporosis therapies in combination. Curr Osteoporos Rep 15:343–352
6. Cummings SR, Black DM, Nevitt MC et al (1993) Bone density at various sites for prediction of hip fractures. The study of osteoporotic fractures research group. Lancet (London, England) 341:72–75
7. Ferrari S, Libanati C, Lin CJF et al (2019) Relationship between bone mineral density T-score and nonvertebral fracture risk over 10 years of denosumab treatment. J Bone Miner Res 34:1033–1040
8. Cosman F, Lewiecki EM, Ebeling PR et al (2020) T-Score as an Indicator of Fracture Risk During Treatment With Romosozumab or Alendronate in the ARCH Trial. J Bone Miner Res. 35:1333–1342
9. Bouxsein ML, Eastell R, Lui LY et al (2019) Change in bone density and reduction in fracture risk: a meta-regression of published trials. J Bone Miner Res 34:632–642
10. Kanis JA, Harvey NC, McCloskey E et al (2020) Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures. Osteoporos Int 31:1–12
11. Kanis JA, Harvey NC, Johansson H et al (2020) A decade of FRAX: how has it changed the management of osteoporosis? Aging Clin Exp Res 32:187–196
12. Minisola S, Cipriani C, Grotta GD et al (2019) Update on the safety and efficacy of teriparatide in the treatment of osteoporosis. Ther Adv Musculoskelet Dis 11:1759720
13. Sleeman A, Clements JN (2019) Abaloparatide: a new pharmacological option for osteoporosis. Am J Health Syst Pharm 76:130–135
14. McClung MR (2018) Romosozumab for the treatment of osteoporosis. Osteoporos Sarcopenia 4:11–15
15. Kaveh S, Hosseinifard H, Ghadimi N et al (2020) Efficacy and safety of Romosozumab in treatment for low bone mineral density: a systematic review and meta-analysis. Clin Rheumatol. https://doi.org/10.1007/s10067-020-04948-1
16. Hodsman AB, Bauer DC, Dempster DW et al (2005) Parathyroid hormone and teriparatide for the treatment of osteoporosis: a review of the evidence and suggested guidelines for its use. Endocr Rev 26:688–703
17. Marcus R (2011) Present at the beginning: a personal reminiscence on the history of teriparatide. Osteoporos Int 22:2241–2248
18. Dobnig H, Turner RT (1997) The effects of programmed administration of human parathyroid hormone fragment (1-34) on bone histomorphometry and serum chemistry in rats. Endocrinology 138:4607–4612
19. Jilka RL (2007) Molecular and cellular mechanisms of the anabolic effect of intermittent PTH. Bone 40:1434–1446
20. Silva BC, Costa AG, Cusano NE et al (2011) Catabolic and anabolic actions of parathyroid hormone on the skeleton. J Endocrinol Invest 34:801–810
21. Bellido T, Saini V, Pajevic PD (2013) Effects of PTH on osteocyte function. Bone 54:250–257
22. Reeve J, Hesp R, Williams D et al (1976) Anabolic effect of low doses of a fragment of human parathyroid hormone on the skeleton in postmenopausal osteoporosis. Lancet (London, England) 1:1035–1038
23. Reeve J, Meunier PJ, Parsons JA et al (1980) Anabolic effect of human parathyroid hormone fragment on trabecular bone in involutional osteoporosis: a multicentre trial. BMJ 280:1340–1344
24. Slovik DM, Neer RM, Potts JT Jr (1981) Short-term effects of synthetic human parathyroid hormone (1-34) administration on bone mineral metabolism in osteoporotic patients. J Clin Invest 68:1261–1271
25. Cosman F, Shen V, Xie F et al (1993) Estrogen protection against bone resorbing effects of parathyroid hormone infusion Assessment by use of biochemical markers. Ann Intern Med 118:337–343

26. Lindsay R, Nieves J, Formica C et al (1997) Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. Lancet 350:550–555
27. Lane NE, Sanchez S, Modin GW et al (1998) Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis. Results of a randomized controlled clinical trial. J Clin Invest 102:1627–1633
28. Neer RM, Arnaud CD, Zanchetta JR et al (2001) Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. New Engl J Med 344:1434–1441
29. Lindsay R, Scheele WH, Neer R et al (2004) Sustained vertebral fracture risk reduction after withdrawal of teriparatide in postmenopausal women with osteoporosis. Arch Intern Med 164:2024–2030
30. Prince R, Sipos A, Hossain A et al (2005) Sustained nonvertebral fragility fracture risk reduction after discontinuation of teriparatide treatment. J Bone Miner Res 20:1507–1513
31. Silverman S, Miller P, Sebba A et al (2013) The direct assessment of nonvertebral fractures in community experience (DANCE) study: 2-year nonvertebral fragility fracture results. Osteoporos Int 24:2309–2317
32. Cosman F, Nieves JW, Zion M et al (2009) Retreatment with teriparatide one year after the first teriparatide course in patients on continued long-term alendronate. J Bone Miner Res 24:1110–1115
33. Finkelstein JS, Wyland JJ, Leder BZ et al (2009) Effects of teriparatide retreatment in osteoporotic men and women. J Clin Endocrinol Metab 94:2495–2501
34. Mana DL, Zanchetta MB, Zanchetta JR (2017) Retreatment with teriparatide: our experience in three patients with severe secondary osteoporosis. Osteoporos Int 28:1491–1494
35. Jiang Y, Zhao JJ, Mitlak BH et al (2003) Recombinant human parathyroid hormone (1-34) [teriparatide] improves both cortical and cancellous bone structure. J Bone Miner Res 18:1932–1941
36. Miller PD, Hattersley G, Riis BJ et al (2016) Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. JAMA 316:722–733
37. Moreira CA, Fitzpatrick LA, Wang Y et al (2016) Effects of abaloparatide-SC (BA058) on bone histology and histomorphometry: the ACTIVE phase 3 trial. Bone 97:314–319
38. Dempster DW, Zhou H, Recker RR et al (2018) Remodeling- and modeling-based bone formation with teriparatide versus denosumab: a longitudinal analysis from baseline to 3 months in the AVA study. J Bone Miner Res 33:298–306
39. Arlot M, Meunier PJ, Boivin G et al (2005) Differential effects of teriparatide and alendronate on bone remodeling in postmenopausal women assessed by histomorphometric parameters. J Bone Miner Res 20:1244–1253
40. Gatti D, Viapiana O, Idolazzi L et al (2011) The waning of teriparatide effect on bone formation markers in postmenopausal osteoporosis is associated with increasing serum levels of DKK1. J Clin Endocrinol Metab 96:1555–1559
41. Jolette J, Attalla B, Varela A et al (2017) Comparing the incidence of bone tumors in rats chronically exposed to the selective PTH type 1 receptor agonist abaloparatide or PTH(1-34). Regul Toxicol Pharmacol 86:356–365
42. Andrews EB, Gilsenan AW, Midkiff K et al (2012) The US postmarketing surveillance study of adult osteosarcoma and teriparatide: study design and findings from the first 7 years. J Bone Miner Res 27:2429–2437
43. Cosman F, Lane NE, Bolognese MA et al (2010) Effect of transdermal teriparatide administration on bone mineral density in postmenopausal women. J Clin Endocrinol Metab 95:151–158
44. Pearson RG, Masud T, Blackshaw E et al (2019) Nasal administration and plasma pharmacokinetics of parathyroid hormone peptide PTH 1-34 for the treatment of osteoporosis. Pharmaceutics 11:265
45. Nakamura T, Sugimoto T, Nakano T et al (2012) Randomized teriparatide [human parathyroid hormone (PTH) 1-34] once-weekly efficacy research (TOWER) trial for examining the reduction in new vertebral fractures in subjects with primary osteoporosis and high fracture risk. J Clin Endocrinol Metab 97:3097–3106
46. Nakano T, Shiraki M, Sugimoto T et al (2014) Once-weekly teriparatide reduces the risk of vertebral fracture in patients with various fracture risks: subgroup analysis of the Teriparatide Once-Weekly Efficacy Research (TOWER) trial. J Bone Min Metab 32:441–446
47. Hagino H, Narita R, Yokoyama Y et al (2019) A multicenter, randomized, rater-blinded, parallel-group, phase 3 study to compare the efficacy, safety, and immunogenicity of biosimilar RGB-10 and reference once-daily teriparatide in patients with osteoporosis. Osteoporos Int 30:2027–2037
48. Pfenex. FDA Approves Bonsity (teriparatide injection) to Treat Osteoporosis (2019). https://www.drugs.com/newdrugs/fda-approves-bonsity-teriparatide-osteoporosis-5072.html. Accessed June 29, 2020
49. Company ELa. FORTEO Presecribing Information (2020). https://uspl.lilly.com/forteo/forteo.html#pi. Accessed June 29, 2020
50. Greenspan SL, Bone HG, Ettinger MP et al (2007) 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 146:326–339
51. Agency EM. Preotact (2014) [updated 02/07/2014. https://www.ema.europa.eu/en/medicines/human/EPAR/preotact. Accessed August 25, 2020
52. Hattersley G, Dean T, Corbin BA et al (2016) Binding selectivity of abaloparatide for PTH-Type-1-receptor conformations and effects on downstream signaling. Endocrinology 157:141–149
53. Bahar H, Gallacher K, Downall J et al (2016) Six weeks of daily abaloparatide treatment increased vertebral and femoral bone mineral density, microarchitecture and strength in ovariectomized osteopenic rats. Calcif Tissue Int 99:489–499
54. Varela A, Chouinard L, Lesage E et al (2017) One year of abaloparatide, a selective activator of the PTH1 receptor, increased bone formation and bone mass in osteopenic ovariectomized rats without increasing bone resorption. J Bone Miner Res 32:24–33
55. Doyle N, Varela A, Haile S et al (2018) Abaloparatide, a novel PTH receptor agonist, increased bone mass and strength in ovariectomized cynomolgus monkeys by increasing bone formation without increasing bone resorption. Osteoporos Int 29:685–697
56. Leder BZ, O'Dea LS, Zanchetta JR et al (2015) Effects of abaloparatide, a human parathyroid hormone-related peptide analog, on bone mineral density in postmenopausal women with osteoporosis. J Clin Endocrinol Metab 100:697–706
57. Cosman F, Hattersley G, Hu MY et al (2017) 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 32:17–23
58. Bilezikian JP, Hattersley G, Mitlak BH et al (2019) Abaloparatide in patients with mild or moderate renal impairment: results from the ACTIVE phase 3 trial. Curr Med Res Opin 35:2097–2102
59. McClung MR, Williams GC, Hattersley G et al (2018) Geography of fracture incidence in postmenopausal women with osteoporosis treated with abaloparatide. Calcif Tissue Int 102:627–633
60. Dhaliwal R, Hans D, Hattersley G et al (2020) Abaloparatide in postmenopausal women with osteoporosis and type 2 diabetes: a post hoc analysis of the ACTIVE study. JBMR Plus 4:e10346

61. Watts NB, Hattersley G, Fitzpatrick LA et al (2019) Abaloparatide effect on forearm bone mineral density and wrist fracture risk in postmenopausal women with osteoporosis. Osteoporos Int 30:1187–1194
62. Reginster J, Bianic F, Campbell R et al (2019) Abaloparatide for risk reduction of nonvertebral and vertebral fractures in postmenopausal women with osteoporosis: a network meta-analysis. Osteoporos Int 30:1465–1473
63. Cosman F, Miller PD, Williams GC et al (2017) 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 92:200–210
64. Bone HG, Cosman F, Miller PD et al (2018) ACTIVExtend: 24 months of alendronate after 18 months of abaloparatide or placebo for postmenopausal osteoporosis. J Clin Endocrinol Metab 103:2949–2957
65. Leder B, Zapalowski C, Hu MY et al (2019) Fracture and bone mineral density response by baseline risk in patients treated with abaloparatide followed by alendronate: results from the phase 3 ACTIVExtend Trial. J Bone Miner Res 34:2213–2219
66. Agency EM. Refusal of the marketing authorisation for Eladynos (abaloparatide) (2017). https://www.ema.europa.eu/en/documents/smop-initial/questions-answers-refusal-marketing-authorisation-eladynos-abaloparatide_en.pdf. Accessed June 29, 2020
67. Health R. TYMLOS Prescribing Information (2018) https://radiuspharm.com/wp-content/uploads/tymlos/tymlos-prescribing-information.pdf. Accessed June 29, 2020
68. Shirley M (2017) Abaloparatide: first Global Approval. Drugs 77:1363–1368
69. Delgado-Calle J, Sato AY, Bellido T (2017) Role and mechanism of action of sclerostin in bone. Bone 96:29–37
70. Ominsky MS, Niu QT, Li C et al (2014) Tissue-level mechanisms responsible for the increase in bone formation and bone volume by sclerostin antibody. J Bone Miner Res 29:1424–1430
71. Ominsky MS, Boyce RW, Li X et al (2017) Effects of sclerostin antibodies in animal models of osteoporosis. Bone 96:63–75
72. Ominsky MS, Boyd SK, Varela A et al (2017) Romosozumab improves bone mass and strength while maintaining bone quality in ovariectomized cynomolgus monkeys. J Bone Miner Res 32:788–801
73. Padhi D, Jang G, Stouch B et al (2011) Single-dose, placebo-controlled, randomized study of AMG 785, a sclerostin monoclonal antibody. J Bone Miner Res 26:19–26
74. Padhi D, Allison M, Kivitz AJ et al (2014) Multiple doses of sclerostin antibody romosozumab in healthy men and postmenopausal women with low bone mass: a randomized, double-blind, placebo-controlled study. J Clin Pharmacol 54:168–178
75. McClung MR, San Martin J, Miller PD et al (2005) Opposite bone remodeling effects of teriparatide and alendronate in increasing bone mass. Arch Intern Med 165:1762–1768
76. McClung MR, Brown JP, Diez-Perez A et al (2018) 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 33:1397–1406
77. Ishibashi H, Crittenden DB, Miyauchi A et al (2017) Romosozumab increases bone mineral density in postmenopausal Japanese women with osteoporosis: a phase 2 study. Bone 103:209–215
78. Stolina M, Dwyer D, Niu QT et al (2014) Temporal changes in systemic and local expression of bone turnover markers during six months of sclerostin antibody administration to ovariectomized rats. Bone 67:305–313
79. Boyce RW, Brown D, Felx M et al (2018) Decreased osteoprogenitor proliferation precedes attenuation of cancellous bone formation in ovariectomized rats treated with sclerostin antibody. Bone Rep 8:90–94
80. Kendler DL, Bone HG, Massari F et al (2019) Bone mineral density gains with a second 12-month course of romosozumab therapy following placebo or denosumab. Osteoporos Int 30:2437–2448
81. Cosman F, Crittenden DB, Adachi JD et al (2016) Romosozumab treatment in postmenopausal women with osteoporosis. New Engl J Med 375:1532–1543
82. Lewiecki EM, Dinavahi RV, Lazaretti-Castro M et al (2019) One year of romosozumab followed by two years of denosumab maintains fracture risk reductions: results of the FRAME extension study. J Bone Miner Res 34:419–428
83. Saag KG, Petersen J, Brandi ML et al (2017) Romosozumab or alendronate for fracture prevention in women with osteoporosis. New Engl J Med 377:1417–1427
84. Chavassieux P, Chapurlat R, Portero-Muzy N et al (2019) Bone-forming and antiresorptive effects of romosozumab in postmenopausal women with osteoporosis: bone histomorphometry and microcomputed tomography analysis after 2 and 12 months of treatment. J Bone Miner Res 34:1597–1608
85. McClung MR, Grauer A, Boonen S et al (2014) Romosozumab in postmenopausal women with low bone mineral density. New Engl J Med 370:412–420
86. Chouinard L, Felx M, Mellal N et al (2016) Carcinogenicity risk assessment of romosozumab: a review of scientific weight-of-evidence and findings in a rat lifetime pharmacology study. Regulat Toxicol Pharmacol 81:212–222
87. Amgen. Bone, Reproductive and Urologic Drugs Advisory Committee for Romosozumab Briefing Materials (2019). https://www.fda.gov/media/121255/download. Accessed June 29, 2020
88. Krishna SM, Seto SW, Jose RJ et al (2017) WNT signaling pathway inhibitor sclerostin inhibits angiotensin ii-induced aortic aneurysm and atherosclerosis. Arterioscler Thromb Vasc Biol 37:553–566
89. Lyles KW, Colon-Emeric CS, Magaziner JS et al (2007) Zoledronic acid and clinical fractures and mortality after hip fracture. New Engl J Med 357:1799–1809
90. Reid IR, Horne AM, Mihov B et al (2018) Fracture prevention with zoledronate in older women with osteopenia. New Engl J Med 379:2407–2416
91. Kim DH, Rogers JR, Fulchino LA et al (2015) Bisphosphonates and risk of cardiovascular events: a meta-analysis. PLoS ONE 10:e0122646
92. Kranenburg G, Bartstra JW, Weijmans M et al (2016) Bisphosphonates for cardiovascular risk reduction: a systematic review and meta-analysis. Atherosclerosis 252:106–115
93. Food and Drug Administration. Bone Reproductive and Urologic Drugs Advisory Committee (BRUDAC) Meeting, January 29 (2019) https://www.fda.gov/media/112946/download. Accessed June 25, 2020
94. Cummings SR, McCulloch C (2020) Explanations for the difference in rates of cardiovascular events in a trial of alendronate and romosozumab. Osteoporos Int 31:1019–1021
95. European Medicines Agency (2019) Human medicine European public assessment report (EPAR): Evenity, pp. 1–263
96. Amgen. EVENITY Prescribing Information (2019). https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/evenity/evenity_pi_hcp_english.ashx. Accessed June 29, 2020
97. Imaz I, Zegarra P, González-Enríquez J et al (2010) Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: systematic review and meta-analysis. Osteoporos Int 21:1943–1951
98. Koller G, Goetz V, Vandermeer B et al (2020) Persistence and adherence to parenteral osteoporosis therapies: a systematic

review. Osteoporos Int. https://doi.org/10.1007/s00198-020-05507-9
99. Body JJ, Gaich GA, Scheele WH et al (2002) A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-34)] with alendronate in postmenopausal women with osteoporosis. J Clin Endocrinol Metab 87:4528–4535
100. Hadji P, Zanchetta JR, Russo L et al (2012) The effect of teriparatide compared with risedronate on reduction of back pain in postmenopausal women with osteoporotic vertebral fractures. Osteoporos Int 23:2141–2150
101. Saag KG, Shane E, Boonen S et al (2007) Teriparatide or alendronate in glucocorticoid-induced osteoporosis. New Engl J Med 357:2028–2039
102. Cosman F, Eriksen EF, Recknor C et al (2011) Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1-34)] in postmenopausal osteoporosis. J Bone Miner Res 26:503–511
103. Leder BZ, Tsai JN, Uihlein AV et al (2014) Two years of Denosumab and teriparatide administration in postmenopausal women with osteoporosis (The DATA Extension Study): a randomized controlled trial. J Clin Endocrinol Metab 99:1694–1700
104. Kendler DL, Marin F, Zerbini CAF et al (2018) 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 (London, England). 391:230–240
105. Miller PD, Hattersley G, Lau E et al (2019) Bone mineral density response rates are greater in patients treated with abaloparatide compared with those treated with placebo or teriparatide: results from the ACTIVE phase 3 trial. Bone 120:137–140
106. Genant HK, Engelke K, Bolognese MA et al (2017) Effects of romosozumab compared with teriparatide on bone density and mass at the spine and hip in postmenopausal women with low bone mass. J Bone Miner Res. 32:181–187
107. Keaveny TM, Crittenden DB, Bolognese MA et al (2017) Greater gains in spine and hip strength for romosozumab compared with teriparatide in postmenopausal women with low bone mass. J Bone Miner Res 32:1956–1962
108. Langdahl BL, Libanati C, Crittenden DB et al (2017) Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial. The Lancet 390:1585–1594
109. Leder BZ, Tsai JN, Uihlein AV et al (2015) Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. Lancet (London, England). 386:1147–1155
110. McClung MR, Bolognese MA, Brown JP et al (2020) A single dose of zoledronate preserves bone mineral density for up to 2 years after a second course of romosozumab. Osteoporos Int. https://doi.org/10.1007/s00198-020-05502-0
111. Cosman F, Crittenden DB, Ferrari S et al (2018) FRAME study: the foundation effect of building bone with 1 year of romosozumab leads to continued lower fracture risk after transition to denosumab. J Bone Miner Res 33:1219–1226
112. Adami S, San Martin J, Munoz-Torres M et al (2008) Effect of raloxifene after recombinant teriparatide [hPTH(1-34)] treatment in postmenopausal women with osteoporosis. Osteoporos Int 19:87–94
113. Eastell R, Nickelsen T, Marin F et al (2009) Sequential treatment of severe postmenopausal osteoporosis after teriparatide: final results of the randomized, controlled European Study of Forsteo (EUROFORS). J Bone Miner Res 24:726–736
114. Minne H, Audran M, Simões ME et al (2008) Bone density after teriparatide in patients with or without prior antiresorptive treatment: one-year results from the EUROFORS study. Curr Med Res Opin 24:3117–3128
115. Boonen S, Marin F, Obermayer-Pietsch B et al (2008) Effects of previous antiresorptive therapy on the bone mineral density response to two years of teriparatide treatment in postmenopausal women with osteoporosis. J Clin Endocrinol Metab 93:852–860
116. Obermayer-Pietsch BM, Marin F, McCloskey EV et al (2008) 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 23:1591–1600
117. Cosman F, Wermers RA, Recknor C et al (2009) Effects of teriparatide in postmenopausal women with osteoporosis on prior alendronate or raloxifene: differences between stopping and continuing the antiresorptive agent. J Clin Endocrinol Metab 94:3772–3780
118. Langdahl BL, Libanati C, Crittenden DB et al (2017) Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial. Lancet (London, England). 390:1585–1594
119. Ravn P, Clemmesen B, Christiansen C (1999) Biochemical markers can predict the response in bone mass during alendronate treatment in early postmenopausal women. Alendronate osteoporosis prevention study group. Bone. 24:237–244
120. Greenspan SL, Schneider DL, McClung MR et al (2002) Alendronate improves bone mineral density in elderly women with osteoporosis residing in long-term care facilities. A randomized, double-blind, placebo-controlled trial. Ann Int Med 136:742–746
121. Chen P, Satterwhite JH, Licata AA et al (2005) Early changes in biochemical markers of bone formation predict BMD response to teriparatide in postmenopausal women with osteoporosis. J Bone Miner Res 20:962–970
122. Cosman F, Keaveny TM, Kopperdahl D et al (2013) 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. 28:1328–1336
123. Stepan JJ, Burr DB, Li J et al (2010) Histomorphometric changes by teriparatide in alendronate-pretreated women with osteoporosis. Osteoporos Int 21:2027–2036
124. Ma YL, Zeng QQ, Chiang AY et al (2014) Effects of teriparatide on cortical histomorphometric variables in postmenopausal women with or without prior alendronate treatment. Bone 59:139–147
125. Fahrleitner-Pammer A, Burr D, Dobnig H et al (2016) Improvement of cancellous bone microstructure in patients on teriparatide following alendronate pretreatment. Bone 89:16–24
126. Miller PD, Bolognese MA, Lewiecki EM et al (2008) Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. Bone 43:222–229
127. Fogelman I, Fordham JN, Fraser WD et al (2008) Parathyroid hormone(1-84) treatment of postmenopausal women with low bone mass receiving hormone replacement therapy. Calcif Tissue Int 83:85–92
128. Deal C, Omizo M, Schwartz EN et al (2005) Combination teriparatide and raloxifene therapy for postmenopausal osteoporosis: results from a 6-month double-blind placebo-controlled trial. J Bone Miner Res 20:1905–1911
129. Tsai JN, Uihlein AV, Lee H et al (2013) Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. Lancet (London, England). 382:50–56
130. Tsai JN, Uihlein AV, Burnett-Bowie SA et al (2015) Comparative effects of teriparatide, denosumab, and combination therapy on

peripheral compartmental bone density, microarchitecture, and estimated strength: the DATA-HRpQCT Study. J Bone Miner Res 30:39–45
131. Tsai JN, Uihlein AV, Burnett-Bowie SM et al (2016) Effects of two years of teriparatide, denosumab, or both on bone microarchitecture and strength (DATA-HRpQCT study). J Clin Endocrinol Metab 101:2023–2030
132. Nakamura Y, Suzuki T, Kamimura M et al (2017) Two-year clinical outcome of denosumab treatment alone and in combination with teriparatide in Japanese treatment-naive postmenopausal osteoporotic women. Bone Res 5:16055
133. Suzuki T, Nakamura Y, Kato H (2019) Efficacy of 4-year denosumab treatment alone or in combination with teriparatide in Japanese postmenopausal osteoporotic women. Mod Rheumatol 29:676–681
134. Tsai JN, Lee H, David NL et al (2019) Combination denosumab and high dose teriparatide for postmenopausal osteoporosis (DATA-HD): a randomised, controlled phase 4 trial. Lancet Diabetes Endocrinol 7:767–775
135. Idolazzi L, Rossini M, Viapiana O et al (2016) Teriparatide and denosumab combination therapy and skeletal metabolism. Osteoporos Int 27:3301–3307
136. Lou S, Lv H, Yin P et al (2019) Combination therapy with parathyroid hormone analogs and antiresorptive agents for osteoporosis: a systematic review and meta-analysis of randomized controlled trials. Osteoporos Int 30:59–70
137. Albert SG, Reddy S (2017) Clinical evaluation and cost efficacy of drugs for treatment of osteoporosis: a meta-analysis. Endocr Pract 23:841–856
138. Mori T, Crandall CJ, Ganz DA (2019) Cost-effectiveness of sequential teriparatide/alendronate versus alendronate-alone strategies in highrisk osteoporotic women in the US: analyzing the impact of generic/biosimilar teriparatide. JBMR Plus 3:e10233
139. Davis S, Simpson E, Hamilton J et al (2020) Denosumab, raloxifene, romosozumab and teriparatide to prevent osteoporotic fragility fractures: a systematic review and economic evaluation. Health Technol Assess 24:1–314
140. Hiligsmann M, Williams SA, Fitzpatrick LA et al (2020) Cost-effectiveness of sequential treatment with abaloparatide followed by alendronate vs. alendronate monotherapy in women at increased risk of fracture: A US payer perspective. Semin Arthr Rheumat. 50:394–400
141. Hiligsmann M, Williams SA, Fitzpatrick LA et al (2019) Cost-effectiveness of sequential treatment with abaloparatide vs. teriparatide for United States women at increased risk of fracture. Seminars Arthritis Rheum. 49:184–196
142. Le QA, Hay JW, Becker R et al (2019) Cost-effectiveness analysis of sequential treatment of abaloparatide followed by alendronate versus teriparatide followed by alendronate in postmenopausal women with osteoporosis in the United States. Ann Pharm 53:134–143
143. Orwoll ES, Scheele WH, Paul S et al (2003) The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. J Bone Miner Res 18:9–17
144. Kaufman JM, Orwoll E, Goemaere S et al (2005) Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. Osteoporos Int 16:510–516
145. Lewiecki EM, Blicharski T, Goemaere S et al (2018) A phase III randomized placebo-controlled trial to evaluate efficacy and safety of romosozumab in men with osteoporosis. J Clin Endocrinol Metab 103:3183–3193
146. Chandler H, Brooks DJ, Hattersley G et al (2019) Abaloparatide increases bone mineral density and bone strength in ovariectomized rabbits with glucocorticoid-induced osteopenia. Osteoporos Int 30:1607–1616
147. Cohen A, Stein EM, Recker RR et al (2013) Teriparatide for idiopathic osteoporosis in premenopausal women: a pilot study. J Clin Endocrinol Metab 98:1971–1981
148. Nishiyama KK, Cohen A, Young P et al (2014) Teriparatide increases strength of the peripheral skeleton in premenopausal women with idiopathic osteoporosis: a pilot HR-pQCT study. J Clin Endocrinol Metab 99:2418–2425
149. Hong N, Kim JE, Lee SJ et al (2018) Changes in bone mineral density and bone turnover markers during treatment with teriparatide in pregnancy- and lactation-associated osteoporosis. Clin Endocrinol 88:652–658
150. Bernhardsson M, Aspenberg P (2018) Abaloparatide versus teriparatide: a head to head comparison of effects on fracture healing in mouse models. Acta Orthop 89:674–677
151. Lanske B, Chandler H, Pierce A et al (2019) Abaloparatide, a PTH receptor agonist with homology to PTHrP, enhances callus bridging and biomechanical properties in rats with femoral fracture. J Orthopaed Res 37:812–820
152. Feng G, Chang-Qing Z, Yi-Min C et al (2015) Systemic administration of sclerostin monoclonal antibody accelerates fracture healing in the femoral osteotomy model of young rats. Int Immunopharmacol 24:7–13
153. Ominsky MS, Li C, Li X et al (2011) Inhibition of sclerostin by monoclonal antibody enhances bone healing and improves bone density and strength of nonfractured bones. JJ Bone Miner Res 26:1012–1021
154. Aspenberg P, Genant HK, Johansson T et al (2010) 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 25:404–414
155. Bhandari M, Schemitsch EH, Karachalios T et al (2020) Romosozumab in skeletally mature adults with a fresh unilateral tibial diaphyseal fracture: a randomized phase-2 study. J Bone Joint Surg Am 102:1416–1426
156. Schemitsch EH, Miclau T, Karachalios T et al (2020) A randomized, placebo-controlled study of romosozumab for the treatment of hip fractures. J Bone Joint Surg Am 102:693–702

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.