

The role of osteoanabolic agents in the management of patients with osteoporosis

Michael R. McClung^a, Micol S. Rothman^b, E. Michael Lewiecki^c, David A. Hanley^d, Steven T. Harris^e, Paul D. Miller^f and David L. Kendler^g

^aOregon Osteoporosis Center, Portland, OR; ^bMary MacKillop Institute for Health Research, Australian Catholic University, Melbourne, Victoria, Australia; ^cDepartment of Medicine, University of Colorado School of Medicine, Aurora, CO, USA; ^dNew Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM, USA; ^eDepartments of Medicine, Community Health Sciences, and Oncology, Cumming School of Medicine and McCaig Institute for Bone and Joint Health, the University of Calgary, Calgary, Alberta, Canada; ^fDepartment of Medicine, University of California, San Francisco, CA, USA; ^gColorado Center for Bone Health, Lakewood, CO, USA; ^hDepartment of Medicine (Endocrinology), University of British Columbia, Vancouver, British Columbia, Canada

ABSTRACT

Reducing fracture risk is the objective of osteoporosis treatment. Bone-forming osteoporosis drugs increase bone mass, restore bone microarchitecture, and reduce fracture risk more effectively than oral bisphosphonates, providing strong justification for the use of these agents as the initial therapy or after anti-remodeling agents in patients at very high risk of fracture. At the end of a 12-to-24-month course of osteoanabolic therapy, transitioning to a potent anti-remodeling agent maintains and enhances the treatment benefit. This review describes the clinical applications of osteoanabolic therapy for osteoporosis.

ARTICLE HISTORY

Received 15 December 2021
Accepted 20 April 2022

KEYWORDS

Osteoporosis; osteoanabolic; abaloparatide; romosozumab; teriparatide; sequence

1. Introduction

Osteoporosis is a chronic disorder characterized by low bone mass and disordered skeletal microarchitecture, resulting in impaired bone strength and an increased risk of fracture [1]. The relatively rapid bone loss that occurs in early menopause in women results in thinning of bone trabeculae, converting thick plates of bone to thin, gracile trabecular rods. With continued bone loss accompanying advancing age, perforation of trabecular struts occurs as well as cortical bone loss, predisposing to vertebral collapse or fracture as well as hip fracture [2]. Approximately 2 million fractures occur in adults in the US each year, including 300,000 hip fractures that are associated with substantial morbidity and mortality [3]. Non-pharmacological strategies may slow the development of osteoporosis but are not adequate management for patients at high fracture risk [4]. Multiple pharmacological treatments are available for osteoporosis, but none cure the disorder. As a result, patients with osteoporosis require long-term, perhaps life-long, individualized management plans, and many patients will require multiple anti-osteoporosis medications during their lifetimes.

Pharmacological therapies for osteoporosis improve bone strength by modulating bone modeling and remodeling. The ideal therapy for osteoporosis would normalize bone strength by restoring the deficit in bone mass and by reconstructing the disordered skeletal architecture. Rebuilding bone structure requires the activation of osteoblastic bone formation. The drugs most commonly used to

treat osteoporosis, including estrogen and estrogen agonists, bisphosphonates and denosumab, are anti-remodeling drugs (often referred to as anti-resorptive agents). They decrease both bone resorption and, to a lesser extent, bone formation, resulting in a positive bone balance, an increase in bone mineral density (BMD) and improved bone strength. However, because they do not stimulate bone formation, they cannot and do not restore the deteriorated microarchitecture of trabecular or cortical bone. Only the osteoanabolic or bone-forming agents, teriparatide, abaloparatide, and romosozumab, stimulate new bone formation, inducing large increases in bone mass and improving cortical and trabecular microarchitecture (Table 1).

Several lines of evidence suggest that these bone-forming agents have important roles in the treatment of patients with osteoporosis, especially for those at very high risk of fracture (to be defined later). Recent studies have demonstrated the superiority of bone-forming therapies over bisphosphonates in reducing fracture risk, resulting in recommendations in both American and European guidelines to use osteoanabolic agents as initial therapy for the treatment of patients with osteoporosis at very high risk of fracture [4–8]. Detailed reviews of the preclinical and clinical experiences with each of the osteoanabolic drugs are available [9–14]. This paper summarizes important efficacy and safety information about each of these drugs and addresses clinical considerations for the use of these agents in the management of patients with osteoporosis.

Table 1. Osteoanabolic agents (from US prescribing information).

	Teriparatide	Abaloparatide	Romosozumab
Dose	20 µg daily	80 µg daily	210 mg once monthly
Indication(s)	Treatment of postmenopausal women with osteoporosis at high risk for fracture or who have failed or are intolerant to other available osteoporosis therapy (1)	Treatment of postmenopausal women with osteoporosis at high risk for fracture	Treatment of postmenopausal women with osteoporosis at high risk for fracture
Route of administration	Subcutaneous injection by the patient with	prefilled pen	Two subcutaneous injections of 105 mg by a healthcare professional
Treatment duration	Use for more than 2 years during a patient's lifetime should only be considered if a patient remains at or has returned to having a high risk for fracture	Use of abaloparatide for more than 2 years during a patient's lifetime is not recommended.	Limit duration of use to 12 monthly doses at a time but no lifetime limit
Refrigerate the drug	Yes	No	Not applicable
Contraindications	Hypersensitivity to teriparatide or its excipients	Hypersensitivity to abaloparatide	Hypocalcemia, sensitivity to romosozumab
Adverse reactions	Arthralgia, pain, nausea	Hypercalciuria, dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain, vertigo	Arthralgia, headache
Warnings and Precautions	Avoid use in patients with increased risk of osteosarcoma [2] Risk of hypercalcemia, urolithiasis, orthostatic hypotension	Not recommended in patients at increased risk for osteosarcoma [2] Risk of hypercalcemia, urolithiasis, orthostatic hypotension	Serious cardiovascular events including cardiovascular death and non-fatal stroke and myocardial infarction Risk of hypocalcemia, osteonecrosis of the jaw; atypical femoral fracture

1. Also indicated for treatment of men with primary or hypogonadal osteoporosis at high risk for fracture and for treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture.

2. Includes patients with open epiphyses, metabolic bone diseases including Paget's disease, bone metastases, or history of skeletal malignancies, prior external beam, or implant radiation therapy involving the skeleton, and hereditary disorders predisposing to osteosarcoma.

2. Osteoanabolic therapies

Teriparatide received approval as a treatment for postmenopausal osteoporosis in 2002, while abaloparatide and romosozumab became available in 2017 and 2019, respectively. Teriparatide and romosozumab are approved in the United States, Canada, and several other countries to treat women with postmenopausal osteoporosis at high risk of fracture. Abaloparatide is approved for the same indication in the United States but is not available in Canada or elsewhere.

Teriparatide and abaloparatide are parathyroid hormone (PTH) receptor agonists that stimulate the parathyroid hormone 1 receptor to activate bone metabolism and, in the kidney, to increase renal calcium absorption [10,11] (Table 1). With both drugs, the number and activity of osteoblasts is increased, stimulating new bone formation, most of which occurs in active bone remodeling sites on trabecular and endocortical bone surfaces (remodeling-based bone formation) [15,16]. The remodeling sites produced by osteoclastic resorption of bone are then filled or even over filled with the new bone. By increasing receptor activator of nuclear factor kappa-B (RANK) ligand production, these drugs also stimulate bone resorption, thus opening new remodeling spaces to be overfilled. This increase in bone resorption, in addition to other possible mechanisms, limits the anabolic effect of both teriparatide and abaloparatide which wane over time.

Teriparatide is a synthetic peptide comprised of the first 34 amino acids of PTH [9,10]. (Table 1) This peptide contains all the known biologic effects of the native hormone PTH 1–84. Biosimilar preparations of teriparatide are now available in the United States. Abaloparatide is a synthetic analog of the first 34 amino acids of PTH-related peptide with 8 amino acid

substitutions in the 20–34 region [11,12]. Abaloparatide was specifically chosen from among many analogues of PTHrP to optimize the bone formation to bone resorption effects of the drug. In clinical studies, the anabolic effect of abaloparatide is maintained compared to teriparatide with less increase in its bone resorbing and calcium mobilizing effects. This allowed abaloparatide to be used at a dose four times higher (80 µg daily) in clinical trials than the dose of teriparatide (20 µg daily), perhaps accounting for differences in skeletal responses between the two drugs [17,18].

Both drugs are currently self-administered by daily subcutaneous injections with pre-filled syringes containing drug for about one month. Once opened, teriparatide syringes require refrigeration while the abaloparatide syringes do not. Cumulative use of these medications was originally limited to 2 years during a patient's lifetime. A recent update in the branded teriparatide prescribing information states that use for more than 2 years may be considered if a patient remains at or has returned to high risk for fracture, while use of abaloparatide for more than 2 years during a patient's lifetime is not recommended [19,20]. A microstructured transdermal system to deliver abaloparatide intradermally is being evaluated. In an early clinical study, administration of abaloparatide 300 µg daily over 12 months did not meet the primary study endpoint of non-inferior BMD responses to injectable abaloparatide [21].

Romosozumab is a humanized monoclonal antibody that inhibits sclerostin, a natural inhibitor of bone formation, produced by osteocytes [13]. (Table 1) Romosozumab increases remodeling-based formation and also stimulates bone formation on trabecular and endocortical surfaces not undergoing

Table 2. BMD changes with osteoanabolic drugs compared to placebo.

Osteoanabolic drug	Study name and reference	Treatment interval	BMD Mean % difference from placebo		
			Lumbar spine	Total hip	Femoral neck
Teriparatide	PFT [22]	~18 months	8.6%	3.6%	3.5%
Abaloparatide	ACTIVE [18]	18 months	10.4%	4.3%	4.0%
Romosozumab	FRAME [23]	12 months	13.3%	6.9%	5.9%

PFT = Pivotal Fracture Trial; ACTIVE – Abaloparatide Comparator Trial In Vertebral Endpoints;

FRAME = Fracture Study in Postmenopausal Women with Osteoporosis

remodeling (modeling-based formation) [22]. In contrast to teriparatide and abaloparatide, romosozumab inhibits RANK ligand, decreasing bone resorption [22,23]. Because the anabolic effect of romosozumab wanes over 12 months of treatment, therapy is limited to 12 monthly doses, with no lifetime exposure limit. Romosozumab is administered by a healthcare provider as two subcutaneous injections totaling 210 mg once monthly for 12 months.

In Phase 3 clinical trials, therapy with each osteoanabolic drug, compared to placebo, resulted in large increases in lumbar spine BMD and smaller, more variable increases in hip BMD [18,24,25]. (Table 2) Vertebral fracture risk was reduced by 65–88%, and reductions in non-vertebral fracture risk were observed with teriparatide and abaloparatide (Figure 1). None of these studies was large enough to demonstrate hip fracture risk reduction, but a meta-analysis of teriparatide clinical trials supports the probability that this drug is effective in preventing hip fractures [26].

BMD continues to increase when patients take an anti-remodeling agent after a course of teriparatide. For example, BMD in the lumbar spine and total hip increased by 9.5% and 2.0%, respectively, after 24 months of treatment with teriparatide alone [27]. Upon transition to denosumab for 2 additional years, the total changes from baseline were 18.3% and 6.6%, respectively [28].

The increased BMD and associated fracture protection observed with abaloparatide and romosozumab, compared to placebo, were maintained for at least 2 years when patients switched to alendronate or denosumab [25,29,30]. In the Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE) and ACTIVEExtend trials, the total BMD increases in the lumbar spine and total hip were 14.4% and 6.4%, respectively, after 18 months of abaloparatide followed by 24 months of alendronate [29]. (Personal communication, Richard Weiss, MD). During the 2 years of alendronate therapy, vertebral fracture risk was 87% lower in the group that had previously received abaloparatide (0.37%) rather than placebo (2.82%).

After 12 months of romosozumab or placebo therapy in the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) study, participants in both treatment groups received open-label denosumab therapy for 24 months [25]. In the romosozumab-to-denosumab group, BMD after 36 months of treatment was 18.1% above the original baseline in the lumbar spine and had increased by 9.4% at the total hip. The risks of new vertebral and non-vertebral fractures were significantly reduced by 66% and 21%, respectively, compared to treatment with placebo for 12 months followed by denosumab for 24 months.

2.1 Comparison with bisphosphonates

Larger increases in BMD, especially in the lumbar spine, are achieved with osteoanabolic therapies over 12–24 months than with bisphosphonates. In the Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH), 4093 women with severe osteoporosis (96% with prevalent vertebral fracture and 9% with recent hip fracture), mean age 74, were randomized to receive romosozumab 210 mg once monthly or alendronate 70 mg once weekly for 1 year [31]. After that year, all women received open-label alendronate for a total median treatment interval of 33 months

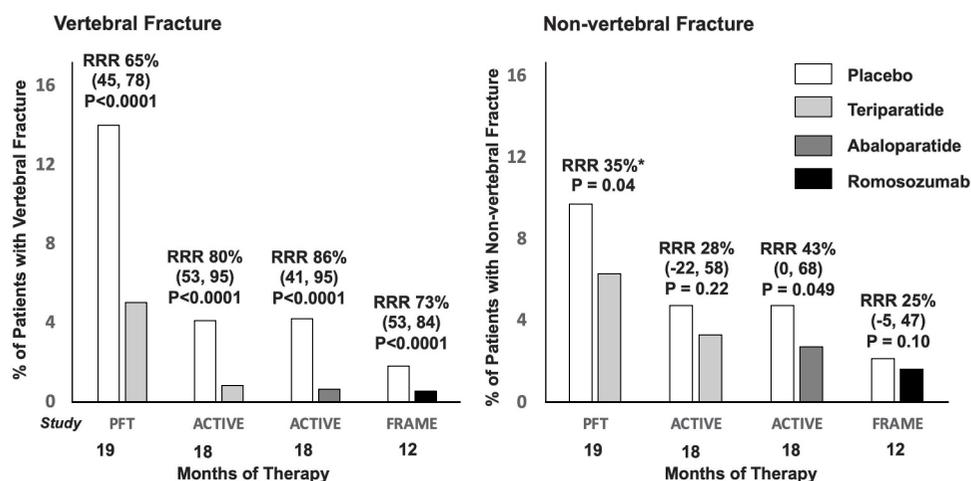


Figure 1. Vertebral and non-vertebral fracture incidence in treatment and placebo groups in separate pivotal trials with osteoanabolic agents in women with postmenopausal osteoporosis. Bar heights denote the incidence of fracture in the placebo and treatment groups. Relative risk reduction with 95% confidence interval is noted for each treatment group. The study names and duration (months) of follow-up are noted for each study. **NOTE:** Because of different patient populations and the different length of follow-up among the studies presented, comparison between studies is not appropriate. * Confidence interval not provided. PFT = Pivotal fracture trial [24]; ACTIVE = Abaloparatide comparator trial in vertebral endpoints trial [18]; FRAME = Fracture study in postmenopausal women with osteoporosis study [25]; RRR = relative risk reduction (95% confidence interval).

in this event-driven trial, and all participants were in the trial for at least 24 months. The average increase in lumbar spine and total hip BMD over 12 months treatment with romosozumab was 13.7% and 6.2%, respectively, while the increases in women assigned to alendronate were 5.0% at the lumbar spine and 2.8% at the total hip. In a subgroup of subjects in ARCH who were monitored with quantitative CT scans, volumetric BMD of the spine increased by 21.9% with romosozumab and by 7.3% with alendronate over 12 months. In that study, estimates of bone strength by finite element analysis (FEA) of the lumbar spine increased by 20.9% and 7.7% with romosozumab and alendronate, respectively [32]. Larger increases in both BMD and estimated bone strength were observed in both cortical and trabecular compartments of the spine. The differences between the two treatment groups persisted for an additional 12 months while women in both groups were receiving open-label alendronate therapy. In a post hoc analysis of the ACTIVE and ACTIVEExtend trials, rates of vertebral fracture were lower with 18 months of abaloparatide therapy (0.47 fractures/100 patient-years) compared to alendronate (1.66 fractures/100 patient-years; relative risk reduction 71%; $P = 0.027$) [33]

Prospective studies have compared the effects of osteoanabolic agents and bisphosphonates on fracture risk reduction. The Vertebral Fracture Treatment Comparisons in Osteoporotic Women (VERO) trial compared teriparatide and risedronate 35 mg weekly for 2 years in women with postmenopausal osteoporosis and previous vertebral fracture (and thus at high fracture risk) [34]. Most (72%) of the patients had previously received osteoporosis therapy. Compared to risedronate, teriparatide significantly reduced vertebral fractures at 12 and 24 months and clinical fractures (painful vertebral fractures and non-vertebral fractures) at 24 months (Table 3). The 34% lower incidence of non-vertebral fractures with teriparatide was not statistically significant. Two smaller studies showed greater reduction in fracture risk with teriparatide compared to either alendronate or risedronate [35,36].

In the ARCH study, romosozumab significantly reduced the incidence of new vertebral fracture by 37% at 12 months compared to alendronate treatment [31] (Table 3). At 24 months, new vertebral fracture risk was still significantly reduced by 48% in patients treated with romosozumab followed by alendronate vs those patients who received 2 years

of alendronate therapy. At the end of the study, nonvertebral fractures were reduced by 19% ($p < 0.04$) and hip fractures by 38% ($p < 0.02$) in patients who received romosozumab for 12 months followed by alendronate compared to those who received only alendronate. Consistent with the ACTIVEExtend and FRAME studies, these results demonstrate that the fracture protection afforded by an osteoanabolic therapy is maintained for at least 2 years upon transitioning to a potent anti-remodeling agent.

2.2 Comparison with denosumab

BMD changes have been compared in separate studies in treatment-naïve women with osteoporosis randomly assigned to receive denosumab or either teriparatide or romosozumab [37,38]. After 12 months, the increase in lumbar spine BMD was greater with romosozumab (12.5%) than with denosumab (7.2%) and was also larger with teriparatide (6.2%) compared to denosumab (5.5%). A different pattern of responses was seen at the total hip. Romosozumab was associated with a larger increase than was seen with denosumab at 12 months (6.0% vs 3.6%) while the increase was greater with denosumab (2.5%) than with teriparatide (0.7%). The significantly larger increase in total hip BMD with denosumab compared to teriparatide persisted during a second year of therapy [27]. Neither of these studies was large enough to compare the fracture efficacy of the osteoanabolic agent and denosumab.

2.3 Adverse events and warnings

In clinical trials, all three osteoanabolic agents were generally well tolerated [18,24,25]. Orthostatic hypotension was described with teriparatide and abaloparatide. Hypercalcemia occurred less commonly with abaloparatide (3.4%) than with teriparatide (6.4%) [18]. Patients with hypercalcemia, bone tumors, bone metastases, or metabolic bone diseases other than osteoporosis and glucocorticoid-induced osteoporosis should not receive these drugs. Because increases in bone tumors were noted in rats exposed to near lifetime exposure to high-dose teriparatide and abaloparatide, the possibility of similar risk in humans was raised [39,40]. Regulatory approvals of both teriparatide and abaloparatide originally included boxed warnings about the possible risk of osteosarcoma.

Table 3. Fracture risk reduction with osteoanabolic agents vs anti-remodeling drugs.

Drug	Teriparatide			Teriparatide			Teriparatide			Romosozumab		
	VERO [32]			Body [33]			Hadji [34]			ARCH [29]		
Study (reference)	24			14			18			12		
Treatment interval (months)	RIS	TPTD	RR (95% CI) P value	ALN	TPTD	RR (95% CI) P value	RIS	TPTD	RR (95% CI) P value	ALN	ROMO	RR (95% CI) P value
Vertebral fracture	12%	5.4%	56% (32, 71%) P = <0.0001	Not provided	Not provided	Not provided	9.4%	4.4%	53%* P = 0.01	6.3%	4.0%	37% (15–53%) P = 0.03
Non-vertebral fracture	6.1%	4.0%	34% (–10 to 61%) P = 0.10	13.7%	4.1%	70%* P = 0.042	8.3%	7.8%	6%* P = 0.89	4.6%	3.4%	26% (–1 to 46%) P = 0.057

* Confidence interval not provided.

VERO = Vertebral Fracture Treatment Comparisons in Osteoporotic Women; ARCH = Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk; RIS = risedronate; TPTD = teriparatide; ALN = alendronate; ROMO = romosozumab; RR = risk reduction; CI = confidence limits.

However, the Forteo Patient Registry study linked more than 75,000 patients who received teriparatide to 42 state cancer registries in the United States, representing more than 93% of the country's population, and none of the 6180 cases of osteosarcoma in the registries matched with a patient who had received teriparatide [41]. In addition, the Osteosarcoma Surveillance Study, a post-marketing study in which patients treated with teriparatide over an interval of 15 years were monitored, revealed that the incidence of osteosarcoma associated with teriparatide use was not higher than the expected background incidence rate of osteosarcoma [42]. This led to the removal of the boxed warning about osteosarcoma from the branded teriparatide label in 2020 but not from the prescribing information for teriparatide biosimilars [19,43]. This was followed by the removal of the boxed warning from the US abaloparatide label in 2021 [44]. The use of these drugs should still be avoided in patients at increased risk for osteosarcoma, including patients with Paget's disease or history of skeletal radiation and children or adolescents with open epiphyses. Abaloparatide is currently available only in the United States. The scientific committee of the European Medicines Agency (EMA) rejected the marketing application for abaloparatide [45].

Romosozumab therapy was associated with mild injection site reactions in 4.4–5.2% of patients compared to 2.6–2.9% in control groups, and hypersensitivity reactions, including rare cases of anaphylaxis, have been described [25,31]. Hypocalcemia upon starting romosozumab therapy has been reported. In the FRAME study, single patients had an atypical femur fracture and an oral adverse event consistent with osteonecrosis of the jaw during 12 months of romosozumab therapy [25].

Because it was known that sclerostin is expressed in vascular smooth muscle, all serious cardiovascular adverse events in the romosozumab Phase 3 studies were reviewed and adjudicated by cardiology specialists. In the ARCH trial, there was a higher risk of major adverse cardiovascular events (MACE; heart attack, stroke, and cardiovascular death) in the first year of therapy with romosozumab (2.0%) vs alendronate (1.1%; hazard ratio 1.87, 95% confidence interval 1.10–3.14), but there was no difference in rates of these events with romosozumab vs placebo in the larger FRAME trial [25,31]. The reason for the difference in cardiovascular risk with romosozumab compared to alendronate in ARCH but not compared to placebo in FRAME is unclear. Although observational studies indicate a possible cardiovascular protective effect of alendronate, the cumulative incidence of MACE over the entirety of the ARCH trial is not consistent with alendronate being protective or romosozumab being harmful [46,47]. Studies in humans and animals do not show an association between sclerostin deficiency and cardiovascular disease [48]. Romosozumab carries a box warning stating that it is not recommended for patients at high risk for cardiovascular events and should not be given to anyone with a myocardial infarction or stroke within the last year.

3. Clinical Questions Regarding Osteoanabolic Therapies

3.1 Who are the best candidates for osteoanabolic therapies?

In theory, all patients with the abnormal bone structure that characterizes osteoporosis would be candidates for treatment to restore that architecture. Recent management guidelines suggest that the use of bone-forming drugs is most appropriate for patients at very high risk of fracture, where the absolute benefit and the cost-effectiveness are the greatest [4,5,7,8]. Examples of patients at very high fracture risk would include individuals who have had multiple or recent (within the past 12 months) fractures, especially a spine or hip fracture; patients with very low BMD (for example, a T-score of <-3.0); and those with very high estimates of fracture risk using FRAX® (e.g. 10 year probability of major osteoporosis fracture >30% or hip fracture >4.5%) or other prediction tools. These recommendations are based upon the superiority of osteoanabolic agents over oral bisphosphonates for fracture risk reduction, especially for vertebral fractures, in the VERO and ARCH studies [31,34]. Because BMD increases are larger with osteoanabolic agents compared to anti-remodeling drugs, beginning therapy with an osteoanabolic agent is the best way to achieve a particular target BMD for patients with very low BMD [49]. As discussed below, osteoanabolic agents can also be considered in patients who have not responded adequately to an anti-remodeling agent [4].

3.2 How does one choose among osteoanabolic agents?

Because direct comparisons of the fracture benefits of osteoanabolic therapies are limited, choosing among the therapies must be based on other information including patient preference [50]. Teriparatide and abaloparatide were directly compared in the abaloparatide Phase 2 study and the ACTIVE trial [17,18]. BMD increases were greater with abaloparatide than with teriparatide (Table 2). While no significant differences in vertebral or non-vertebral fracture risk were observed between the two drugs, the reduction in risk of major osteoporotic fractures was significantly greater with abaloparatide (78%) than with teriparatide (23%) in women at high fracture risk ($p = 0.007$) (Table 4). Adverse event profiles were similar between the two drugs except that hypercalcemia was reported more often with teriparatide than with abaloparatide.

There are no direct comparisons of fracture risk reduction between romosozumab and teriparatide or abaloparatide. Separate studies have demonstrated larger increases in BMD and estimated bone strength with romosozumab compared to teriparatide in treatment-naïve women and in women previously treated with bisphosphonates [23,51,52] (Table 4). Safety profiles between teriparatide and romosozumab were similar except for more hypercalcemia with the former drug and more injection site reactions with romosozumab [52]. Patients should be informed about avoiding the use of teriparatide and abaloparatide in patients at risk for osteosarcoma

Table 4. Direct comparisons of changes in BMD and estimates of bone strength with osteoanabolic agents.

Clinical studies (Reference)	Study participants	Duration of therapy	Measurement	Measurement site	Mean % change from baseline (SD or 95% CI)	
					Teriparatide	Abaloparatide
Teriparatide vs abaloparatide						
Phase 2 study [45]	Treatment-naïve women with low bone density	24 weeks	BMD	Lumbar spine	5.5% (4.1%)	6.7% (4.2%)
				Total hip	0.5% (3.9%)	2.6% (3.5%)
ACTIVE trial [18]	Treatment-naïve women with postmenopausal osteoporosis	18 months	BMD	Lumbar spine	10.5%	11.2%
				Total hip	3.3%	4.2%
Teriparatide vs romosozumab						
Phase 2 study [21, 46]	Treatment-naïve women with low bone density	12 months	BMD	Lumbar spine	7.1% (6.1, 8.2%)	11.3% (10.3, 12.4%)
				Total hip	1.3% (0.7, 2.0%)	4.1% (3.5, 4.8%)
				Estimated strength by FEA Lumbar spine	18.5%	27.3%
				Total hip	-0.7%	3.5%
STRUCTURE study [47]	Bisphosphonate-treated women with low bone density	12 months	BMD	Lumbar spine	5.4% (4.7, 6.1)	9.8% (9.0, 10.5)
				Total hip	-0.5% (-1.0, -0.2%)	2.9% (2.2, 3.0%)
				Estimated strength by FEA Lumbar spine	NA	NA
				Total hip	-0.7% (-1.5, -0.1)	2.5% (1.7, 3.2%)

SD = standard deviation; CI = confidence interval; BMD = bone mineral density; FEA = finite element analysis from computed tomography scans; NA = not available

and of romosozumab in patients at high risk of cardiovascular disease.

Other factors including previous antiresorptive therapy, baseline bone turnover, BMD as well as estimated fracture risk might also influence the choice of the drug. Cost, coverage by insurance, convenience of administration and length of clinical experience may influence patient choice.

3.3 What should be done at the end of a course of osteoanabolic therapy?

The salutary effects of osteoanabolic agents are lost when treatment is stopped. BMD values fall toward or to baseline within several months after discontinuation of teriparatide or romosozumab [53,54]. A potent anti-remodeling drug, either a bisphosphonate or denosumab, should be used to maintain the skeletal benefits of the bone-forming agent, even in patients whose BMD is no longer in the osteoporosis range [4,5,55]. As noted above, the gains in BMD and reductions in fracture risk acquired during osteoanabolic treatment are maintained when patients are transitioned to either alendronate or denosumab. The additional BMD gains observed with denosumab following teriparatide or romosozumab appear to be somewhat greater than the increases seen with alendronate [25,30,31,56,57]. Raloxifene, a weaker anti-remodeling drug, was not able to prevent bone loss when teriparatide was stopped [53].

3.4 Should osteoanabolic agents be used before or after an anti-remodeling drug?

Except for the VERO trial referenced above, we have no information about the effects of osteoanabolic therapies

on fracture risk in patients were previously on other osteoporosis therapies. In addition, BMD responses to teriparatide and romosozumab are greater when given before an anti-remodeling drug compared to the opposite sequence [52,57,58]. These differences likely have important clinical implications. Higher BMD levels achieved on treatment with alendronate, denosumab, and romosozumab are strongly associated with greater reduction in fracture risk [59,60]. These observations are supported by meta-regression analyses showing that therapies resulting in larger increases in BMD are associated with the greater reductions in fracture risk [61,62]. Taken together with the maintenance of BMD and fracture risk benefits when bone building treatments are followed by a bisphosphonate or denosumab, these results suggest that the optimal sequence of treatment is an osteoanabolic agent followed by a potent anti-remodeling drug, particularly for patients at very high risk of fracture, as recommended in recent guidelines [4,5,7,8]. Osteoanabolic agents should also be considered for patients remaining at high risk of fracture after several years of bisphosphonate therapy. Using teriparatide after denosumab is not recommended because that sequence of drugs is associated with transient or progressive bone loss, especially in the hip region [28]. For patients taking denosumab in whom teriparatide therapy is thought to be appropriate, adding teriparatide while continuing denosumab rather than switching therapies could be considered [63]. The limited data evaluating the effects of romosozumab use after denosumab therapy suggest that bone density is maintained during the 12 months of romosozumab therapy although the increase in markers of bone resorption that occur upon denosumab discontinuation was not completely inhibited [58,64].

3.5 Can osteoanabolic agents be used in men with osteoporosis or glucocorticoid-induced osteoporosis?

Teriparatide is the only osteoanabolic agent with current regulatory approval to treat men with osteoporosis and patients with osteoporosis associated with sustained systemic glucocorticoid therapy who are at high risk for fracture. In men with idiopathic and hypogonadal osteoporosis, both teriparatide and romosozumab increased BMD, and teriparatide therapy, for an average of 11 months, reduced vertebral fracture risk by 53% [65–67]. Preliminary results demonstrate BMD increases with abaloparatide in men with osteoporosis [68]. In patients receiving glucocorticoids, teriparatide increased BMD and reduced vertebral fracture risk more than did alendronate at 18 and 36 months [69,70]. The effects of abaloparatide and romosozumab in patients receiving glucocorticoids have not yet been evaluated.

3.6 What is the best way to monitor patients on osteoanabolic agents?

Patients who receive abaloparatide, teriparatide or romosozumab can be assessed with bone mineral density annually or at the end of a course of treatment. Since, as mentioned previously, BMD measured on treatment correlates with a patient's current fracture risk, bone density values after osteoanabolic drug therapy can help guide the choice of the anti-remodeling agent as well as duration of treatment. Experts differ on the use of bone turnover markers to monitor osteoporosis treatment. Many advocate for measuring P1NP as a marker of bone formation and serum C telopeptide of Type I collagen (CTX) as a marker of bone resorption [71,72]. An increase of > 10 mcg/L in P1NP measured 1–3 months after initiation of osteoanabolic treatment is considered a positive response to treatment [73]. When considering which patients at high risk of fracture might benefit from more than 2 years of teriparatide, some have advocated checking serum levels of P1NP [19]. Elevated values suggest ongoing bone formation and thus, an indication to extend the treatment course.

3.7 Can these treatments be used in combination with anti-remodeling drugs?

Simultaneous treatment with teriparatide and oral or IV bisphosphonates provides little added improvement in BMD after 12 months compared to monotherapy [74]. Larger BMD increases over 12 months are observed when teriparatide and denosumab are used together compared to using each drug alone [37,63]. Continuing combined therapy for a second year did not result in greater improvement compared to single drug treatment [27]. No safety issues were identified with the combined therapy, although there were only about 30 patients in each treatment group. The study was too small to know if the greater increase in BMD with the use of the treatments together was associated with a greater reduction in fracture risk. No studies have evaluated the combination of abaloparatide or romosozumab with anti-remodeling drugs.

3.7.1 Can patients be re-treated with an osteoanabolic agent?

The bone-forming effects of teriparatide and romosozumab decrease with continuous treatment [18,54]. After being off treatment for 12 months, large increases in BMD have been seen on retreatment with romosozumab and teriparatide [75,76]. Current regulatory guidance in the United States allows for re-treatment with branded teriparatide if a patient remains or returns to high fracture risk [19]. There is no regulatory restriction on the use of repeat courses of romosozumab. Multiple courses of osteoanabolic therapy, interspersed with treatment with an anti-remodeling drug, are sometimes used by osteoporosis specialists for patients who continue to be at very high risk for fracture.

3.8 What are the effects of osteoanabolic therapy on fracture healing and spinal surgery outcomes?

No adverse effect on fracture healing has been reported with any osteoanabolic drug [77,78]. Consequently, there is no need to delay beginning treatment or to stop treatment in patients with a recent fracture. Patients with recent fractures are often at very high risk of fracture, making them candidates for therapy with an osteoanabolic agent without delay [4,7,79].

In animal studies, including subhuman primates, each of the bone-building drugs has been associated with accelerated fracture healing [80–83]. Case reports have suggested benefit from teriparatide therapy for patients with pelvic, sacral, metatarsal and other fractures [84–87]. However, those results have not been replicated in prospective clinical trials. In a post hoc analysis of a clinical trial evaluating the effect of teriparatide therapy on healing of Colles' fractures, the time to healing was significantly shorter with teriparatide 20 ug daily (7.4 weeks) vs placebo (9.1 weeks) although the primary endpoint of the study (teriparatide 40 ug daily vs placebo) did not reach statistical significance [88]. No improvement was observed, compared to a placebo group, in radiographic healing of pelvic fractures, although improved physical performance was noted in the teriparatide group [89]. Romosozumab treatment of patients after hip or tibial fractures did not demonstrate a beneficial effect on fracture healing [78,90]. The effects of abaloparatide on fracture healing in humans have not been evaluated.

Teriparatide has been proposed as a treatment to aid healing of osteonecrosis of the jaw (ONJ) and atypical femoral fractures associated with bisphosphonate therapy [91–93]. Data of modest quality support the use of teriparatide, especially in combination with antimicrobial therapy, to promote healing of ONJ [94,95]. However, evidence supporting the use of teriparatide to promote healing of atypical femoral fractures is much less strong [96]. Romosozumab treatment after ONJ or an atypical fracture has not been evaluated. Meta-analyses of studies assessing the effects of teriparatide in patients undergoing spinal fusion surgery demonstrate a 2-fold higher likelihood of fusion compared to patients receiving bisphosphonates or no treatment, and teriparatide was associated with a significant decrease in vertebral fractures after

the surgery. [97,98] Neither abaloparatide nor romosozumab has been studied with spinal surgery.

4. Summary

Patients at high or very high risk of fracture can be readily identified on the basis of clinical risk factors and BMD testing. Once these patients are identified, the primary goal of therapy is to reduce fracture risk by strengthening the skeleton and reducing the risk of falls and injuries. By stimulating new bone formation, osteoanabolic drugs address both of the major skeletal components of osteoporosis by increasing BMD more quickly and usually to a greater extent than anti-remodeling drugs and by repairing and restoring the disordered trabecular and cortical bone microarchitecture. Osteoanabolic drugs reduce fracture risk more rapidly and more effectively than do oral bisphosphonates, and the fracture reducing benefits of osteoanabolic agents persist for at least two years after patients transition to an anti-remodeling drug. For these reasons, beginning treatment with an osteoanabolic agent, instead of a bisphosphonate or denosumab, is appropriate for patients at very high risk of fracture who need therapy to increase bone mass and reduce fracture risk rapidly. Because osteoporosis is a chronic condition requiring life-long management, all patients should receive a potent anti-remodeling drug at the end of their 12-to-24-month course of osteoanabolic therapy to maintain bone density and fracture protection.

Acknowledgements

None stated.

Disclosure statement

Michael R. McClung receives consulting fees for Advisory Boards and honorarium for speaking from Amgen. Micol S. Rothman has received consulting fees from AbbVie Pharmaceuticals. E. Michael Lewiecki has received institutional research grant support from Radius, Amgen, Mereo and Bindex; consulting fees for advisory Boards from Amgen, Radius, Alexion, Sandoz and Samsung Bioepis; and honorarium for speaking from Radius and Alexion; and royalties from UpToDate. David A. Hanley has received institutional research grant support and honorarium for speaking from Amgen and Eli Lilly. Steven T. Harris has received honorarium for speaking from Amgen, Eli Lilly and Radius Health and consulting fees for Advisory Boards of Amgen and Radius Health. Paul D. Miller has received institutional research grant support from Amgen, Radius Health, Regeneron, Ultragenyx, National Bone Health Alliance, Immunodiagnostics, and Roche Diagnostics; he has received consulting fees for Advisory Boards of Amgen, Radius Health, Ultragenyx, National Bone Health Alliance and Sandoz. David L. Kendler has received institutional research grant support and honorarium for speaking from Amgen, Pfizer, AstraZeneca Radius Health and Eli Lilly. The authors have no other relevant conflicts of interest to disclose. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Funding

The Western Osteoporosis Alliance received an unrestricted grant from Radius Health to support this project. The sponsors of this project had no role in any aspect of preparing this review.

ORCID

Paul D. Miller  <http://orcid.org/0000-0003-3892-1553>

References

1. Compston JE, McClung MR, Leslie WD. Osteoporosis. *Lancet*. 2019;393(10169):364–376.
2. Kendler DL, Bauer DC, Davison KS, et al. Vertebral fractures: clinical importance and management. *Am J Med*. 2016;129(2):221 e1–10.
3. Lewiecki EM, Ortendahl JD, Vanderpuye-Orgle J, et al. Healthcare policy changes in osteoporosis can improve outcomes and reduce costs in the United States. *JBMR Plus*. 2019;3(9):e10192.
4. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College Of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 update. *Endocr Pract*. 2020;26 (Suppl 1):1–46.
5. Shoback D, Rosen CJ, Black DM, et al. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society guideline update. *J Clin Endocrinol Metab*. 2020;105 (3):587–594.
6. Lewiecki EM, Binkley N, Clark P, et al. Core principles for fracture prevention: North American consensus from the National Osteoporosis Foundation, Osteoporosis Canada, and Academia Nacional de Medicina de Mexico. *Osteoporos Int*. 2020;31 (11):2073–2076.
7. Kanis JA, Harvey NC, McCloskey E, et al. Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures. *Osteoporos Int*. 2020;31(1):1–12.
8. Kanis JA, Johansson H, Harvey NC, et al. An assessment of intervention thresholds for very high fracture risk applied to the NOGG guidelines: a report for the National Osteoporosis Guideline Group (NOGG). *Osteoporos Int*. 2021;32(10):1951–1960.
9. Hodsman AB, Bauer DC, Dempster DW, et al. Parathyroid hormone and teriparatide for the treatment of osteoporosis: a review of the evidence and suggested guidelines for its use. *Endocr Rev*. 2005;26 (5):688–703.
10. Minisola S, Cipriani C, Grotta GD, et al. Update on the safety and efficacy of teriparatide in the treatment of osteoporosis. *Ther Adv Musculoskelet Dis*. 2019;11:1759720X19877994.
11. Miller PD, Bilezikian JP, Fitzpatrick LA, et al. Abaloparatide: an anabolic treatment to reduce fracture risk in postmenopausal women with osteoporosis. *Curr Med Res Opin*. 2020;36 (11):1861–1872.
12. Brent MB. Abaloparatide: a review of preclinical and clinical studies. *Eur J Pharmacol*. 2021;909:174409.
13. McClung MR. Clinical utility of anti-sclerostin antibodies. *Bone*. 2017;96:3–7.
14. Kaveh S, Hosseinifard H, Ghadimi N, et al. Efficacy and safety of romosozumab in treatment for low bone mineral density: a systematic review and meta-analysis. *Clin Rheumatol*. 2020;39 (11):3261–3276.
15. Dempster DW, Zhou H, Ruff VA, et al. Longitudinal effects of teriparatide or zoledronic acid on bone modeling- and remodeling-based formation in the SHOTZ study. *J Bone Miner Res*. 2018;33(4):627–633.
16. Dempster DW, Zhou H, Rao SD, et al. Early effects of abaloparatide on bone formation and resorption indices in postmenopausal women with osteoporosis. *J Bone Miner Res*. 2021;36 (4):644–653.
17. Leder BZ, O'Dea LS, Zanchetta JR, et al. Effects of abaloparatide, a human parathyroid hormone-related peptide analog, on bone mineral density in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab*. 2015;100(2):697–706.
18. Miller PD, Hattersley G, Riis BJ, et al. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. *JAMA*. 2016;316(7):722–733.

19. Miller PD, Lewiecki EM, Krohn K, et al. Teriparatide: label changes and identifying patients for long-term use. *Cleve Clin J Med*. 2021;88(9):489–493.
20. Radius Health. TYMLOS Prescribing Information 2018 Accessed 28 March 2022 Available from: <https://radiuspharm.com/wp-content/uploads/tymlos/tymlos-prescribing-information.pdf>
21. Radius Health. Radius announces results from the wearABLE Trial evaluating abaloparatide transdermal system in postmenopausal women with osteoporosis 2021 Accessed 28 March 2022. Available from: <https://ir.radiuspharm.com/news-releases/news-release-details/radius-announces-results-wearable-trial-evaluating-abaloparatide>
22. Chavassieux P, Chapurlat R, Portero-Muzy N, et al. 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*. 2019;34(9):1597–1608.
23. McClung MR, Grauer A, Boonen S, et al. Romosozumab in postmenopausal women with low bone mineral density. *N Engl J Med*. 2014;370(5):412–420.
24. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med*. 2001;344(19):1434–1441.
25. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med*. 2016;375(16):1532–1543.
26. Diez-Perez A, Marin F, Eriksen EF, et al. Effects of teriparatide on hip and upper limb fractures in patients with osteoporosis: a systematic review and meta-analysis. *Bone*. 2019;120:1–8.
27. Leder BZ, Tsai JN, Uihlein AV, et al. Two years of denosumab and teriparatide administration in postmenopausal women with osteoporosis (the DATA Extension study): a randomized controlled trial. *J Clin Endocrinol Metab*. 2014;99(5):1694–1700.
28. Leder BZ, Tsai JN, Uihlein AV, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. *Lancet*. 2015;386(9999):1147–1155.
29. Bone HG, Cosman F, Miller PD, et al. ACTIVEExtend: 24 months of alendronate after 18 months of abaloparatide or placebo for postmenopausal osteoporosis. *J Clin Endocrinol Metab*. 2018;103(8):2949–2957.
30. Lewiecki EM, Dinavahi RV, Lazaretti-Castro M, et al. One year of romosozumab followed by two years of denosumab maintains fracture risk reductions: results of the FRAME Extension study. *J Bone Miner Res*. 2019;34(3):419–428.
31. Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med*. 2017;377(15):1417–1427.
32. Brown JP, Engelke K, Keaveny TM, et al. Romosozumab improves lumbar spine bone mass and bone strength parameters relative to alendronate in postmenopausal women: results from the active-controlled fracture study in postmenopausal women with osteoporosis at high risk (ARCH) trial. *J Bone Miner Res*. 2021;36(11):2139–2152.
33. Leder BZ, Mitlak B, Hu MY, et al. Effect of abaloparatide vs alendronate on fracture risk reduction in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab*. 2020;105(3):938–943.
34. Kendler DL, Marin F, Zerbini CAF, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet*. 2018;391(10117):230–240.
35. Body JJ, Gaich GA, Scheele WH, et al. 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*. 2002;87(10):4528–4535.
36. Hadji P, Zanchetta JR, Russo L, et al. The effect of teriparatide compared with risedronate on reduction of back pain in postmenopausal women with osteoporotic vertebral fractures. *Osteoporos Int*. 2012;23(8):2141–2150.
37. Tsai JN, Uihlein AV, Lee H, et al. Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. *Lancet*. 2013;382(9886):50–56.
38. Kobayakawa T, Miyazaki A, Saito M, et al. Denosumab versus romosozumab for postmenopausal osteoporosis treatment. *Sci Rep*. 2021;11(1):11801.
39. Vahle JL, Long GG, Sandusky G, et al. Bone neoplasms in F344 rats given teriparatide [rhPTH(1-34)] are dependent on duration of treatment and dose. *Toxicol Pathol*. 2004;32(4):426–438.
40. Jollette J, Attalla B, Varela A, et al. 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*. 2017;86:356–365.
41. Gilsenan A, Harris D, Reynolds M, et al. Long-term cancer surveillance: results from the Forteo patient registry surveillance study. *Osteoporos Int*. 2021;32(4):645–651.
42. Gilsenan A, Midkiff K, Harris D, et al. Teriparatide did not increase adult osteosarcoma incidence in a 15-year US postmarketing surveillance study. *J Bone Miner Res*. 2021;36(2):244–251.
43. Kellier-Steele N, Casso D, Anderson A, et al. Assessing the incidence of osteosarcoma among teriparatide-treated patients using linkage of commercial pharmacy and state cancer registry data, contributing to the removal of boxed warning and other labeling changes. *Bone*. 2022;160:116394.
44. Radius Health. Radius announces update on TYMLOS® (abaloparatide) label. 2021 Accessed 28 March 2022. Available from: <https://ir.radiuspharm.com/news-releases/news-release-details/radius-announces-update-tymlosr-abaloparatide-label>
45. European Medicines Agency. Refusal of the marketing authorisation for Eladynos (abaloparatide). 2017 Accessed 28 March 2022 Available from: https://www.ema.europa.eu/en/documents/smop-initial/questions-answers-refusal-marketing-authorisation-eladynos-abaloparatide_en.pdf
46. Rodriguez AJ, Ernst MT, Nybo M, et al. Oral bisphosphonate use reduces cardiovascular events in a cohort of Danish patients referred for bone mineral density. *J Clin Endocrinol Metab*. 2020;105(10):3215–3225.
47. Cummings SR, McCulloch C. Explanations for the difference in rates of cardiovascular events in a trial of alendronate and romosozumab. *Osteoporos Int*. 2020;31(6):1019–1021.
48. Turk JR, Deaton AM, Yin J, et al. Nonclinical cardiovascular safety evaluation of romosozumab, an inhibitor of sclerostin for the treatment of osteoporosis in postmenopausal women at high risk of fracture. *Regul Toxicol Pharmacol*. 2020;115:104697.
49. Lewiecki EM, Kendler DL, Davison KS, et al. Western Osteoporosis Alliance clinical practice series: treat-to-target for osteoporosis. *Am J Med*. 2019;132(11):e771–e7.
50. Curtis EM, Reginster JY, Al-Daghri N, et al. Management of patients at very high risk of osteoporotic fractures through sequential treatments. *Aging Clin Exp Res*. 2022;34(4):695–714.
51. Keaveny TM, Crittenden DB, Bolognese MA, et al. Greater gains in spine and hip strength for romosozumab compared with teriparatide in postmenopausal women with low bone mass. *J Bone Miner Res*. 2017;32(9):1956–1962.
52. Langdahl BL, Libanati C, Crittenden DB, et al. Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial. *Lancet*. 2017;390(10102):1585–1594.
53. Adami S, San Martin J, Munoz-Torres M, et al. Effect of raloxifene after recombinant teriparatide [hPTH(1-34)] treatment in postmenopausal women with osteoporosis. *Osteoporos Int*. 2008;19(1):87–94.
54. McClung MR, Brown JP, Diez-Perez A, et al. Effects of 24 months of treatment with romosozumab followed by 12 months of denosumab or placebo in postmenopausal women with low bone mineral density: a randomized, double-blind, phase 2, parallel group study. *J Bone Miner Res*. 2018;33(8):1397–1406.

55. Lewiecki EM, Binkley N, Bilezikian JP. Treated osteoporosis is still osteoporosis. *J Bone Miner Res.* 2019;34(4):605–606.
56. Cosman F, Wermers RA, Recknor C, et al. Effects of teriparatide in postmenopausal women with osteoporosis on prior alendronate or raloxifene: differences between stopping and continuing the anti-resorptive agent. *J Clin Endocrinol Metab.* 2009;94(10):3772–3780.
57. Minne H, Audran M, Simoes ME, et al. Bone density after teriparatide in patients with or without prior antiresorptive treatment: one-year results from the EUROFORs study. *Curr Med Res Opin.* 2008;24(11):3117–3128.
58. McClung MR, Bolognese MA, Brown JP, et al. Skeletal responses to romosozumab after 12 months of denosumab. *JBMR Plus.* 2021;5(7):e10512.
59. Ferrari S, Libanati C, Lin CJF, et al. Relationship between bone mineral density T-score and nonvertebral fracture risk over 10 years of denosumab treatment. *J Bone Miner Res.* 2019;34(6):1033–1040.
60. Cosman F, Lewiecki EM, Ebeling PR, et al. T-score as an indicator of fracture risk during treatment with romosozumab or alendronate in the ARCH trial. *J Bone Miner Res.* 2020;35(7):1333–1342.
61. Bouxsein ML, Eastell R, Lui LY, et al. Change in bone density and reduction in fracture risk: a meta-regression of published trials. *J Bone Miner Res.* 2019;34(4):632–642.
62. Black DM, Bauer DC, Vittinghoff E, et al. Treatment-related changes in bone mineral density as a surrogate biomarker for fracture risk reduction: meta-regression analyses of individual patient data from multiple randomised controlled trials. *Lancet Diabetes Endocrinol.* 2020;8(8):672–682.
63. Idolazzi L, Rossini M, Viapiana O, et al. Teriparatide and denosumab combination therapy and skeletal metabolism. *Osteoporos Int.* 2016;27(11):3301–3307.
64. Ebina K, Tsuboi H, Nagayama Y, et al. Effects of prior osteoporosis treatment on 12-month treatment response of romosozumab in patients with postmenopausal osteoporosis. *Joint Bone Spine.* 2021;88(5):105219.
65. Orwoll ES, Scheele WH, Paul S, et al. The effect of teriparatide [human parathyroid hormone (1–34)] therapy on bone density in men with osteoporosis. *J Bone Miner Res.* 2003;18(1):9–17.
66. Kaufman JM, Orwoll E, Goemaere S, et al. Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. *Osteoporos Int.* 2005;16(5):510–516.
67. Lewiecki EM, Blicharski T, Goemaere S, et al. A phase III randomized placebo-controlled trial to evaluate efficacy and safety of romosozumab in men with osteoporosis. *J Clin Endocrinol Metab.* 2018;103(9):3183–3193.
68. Radius Health. Radius announces positive phase 3 topline results for TYMLOS® (abaloparatide) subcutaneous injection in males with osteoporosis Accessed 28 March 2022. Available from: <https://ir.radiuspharm.com/news-releases/news-release-details/radius-announces-positive-phase-3-topline-results-tymlosr>
69. Saag KG, Shane E, Boonen S, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. *N Engl J Med.* 2007;357(20):2028–2039.
70. Saag KG, Zanchetta JR, Devogelaer JP, et al. Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial. *Arthritis Rheum.* 2009;60(11):3346–3355.
71. Vasikaran S, Eastell R, Bruyere O, et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. *Osteoporos Int.* 2011;22(2):391–420.
72. Eastell R, Szulc P. Use of bone turnover markers in postmenopausal osteoporosis. *Lancet Diabetes Endocrinol.* 2017;5(11):908–923.
73. Kregge JH, Lane NE, Harris JM, et al. PINP as a biological response marker during teriparatide treatment for osteoporosis. *Osteoporos Int.* 2014;25(9):2159–2171.
74. McClung MR. Using osteoporosis therapies in combination. *Curr Osteoporos Rep.* 2017;15(4):343–352.
75. Kendler DL, Bone HG, Massari F, et al. Bone mineral density gains with a second 12-month course of romosozumab therapy following placebo or denosumab. *Osteoporos Int.* 2019;30(12):2437–2448.
76. Cosman F, Nieves JW, Zion M, et al. Retreatment with teriparatide one year after the first teriparatide course in patients on continued long-term alendronate. *J Bone Miner Res.* 2009;24(6):1110–1115.
77. Borges JL. Accelerated fracture healing with teriparatide. *Arch Endocrinol Metab.* 2015;59(1):89.
78. Schemitsch EH, Miclau T, Karachalios T, et al. A randomized, placebo-controlled study of romosozumab for the treatment of hip fractures. *J Bone Joint Surg Am.* 2020;102(8):693–702.
79. Balasubramanian A, Zhang J, Chen L, et al. Risk of subsequent fracture after prior fracture among older women. *Osteoporos Int.* 2019;30(1):79–92.
80. Bernhardsson M, Aspenberg P. Abaloparatide versus teriparatide: a head to head comparison of effects on fracture healing in mouse models. *Acta Orthop.* 2018;89(6):674–677.
81. Lanske B, Chandler H, Pierce A, et al. Abaloparatide, a PTH receptor agonist with homology to PTHrP, enhances callus bridging and biomechanical properties in rats with femoral fracture. *J Orthop Res.* 2019;37(4):812–820.
82. Feng G, Chang-Qing Z, Yi-Min C, et al. Systemic administration of sclerostin monoclonal antibody accelerates fracture healing in the femoral osteotomy model of young rats. *Int Immunopharmacol.* 2015;24(1):7–13.
83. Hamann C, Rauner M, Hohna Y, et al. Sclerostin antibody treatment improves bone mass, bone strength, and bone defect regeneration in rats with type 2 diabetes mellitus. *J Bone Miner Res.* 2013;28(3):627–638.
84. Moon SW, Lee DH, Kim YC, et al. Parathyroid hormone 1–34 (teriparatide) treatment in pelvic insufficiency fractures - a report of two cases. *J Bone Metab.* 2012;19(2):147–151.
85. Yoo JI, Ha YC, Ryu HJ, et al. Teriparatide treatment in elderly patients with sacral insufficiency fracture. *J Clin Endocrinol Metab.* 2017;102(2):560–565.
86. Raghavan P, Christofides E. Role of teriparatide in accelerating metatarsal stress fracture healing: a case series and review of literature. *Clin Med Insights Endocrinol Diabetes.* 2012;5:39–45.
87. Kim SM, Kang KC, Kim JW, et al. Current role and application of teriparatide in fracture healing of osteoporotic patients: a systematic review. *J Bone Metab.* 2017;24(1):65–73.
88. Aspenberg P, Genant HK, Johansson T, et al. Teriparatide for acceleration of fracture repair in humans: a prospective, randomized, double-blind study of 102 postmenopausal women with distal radial fractures. *J Bone Miner Res.* 2010;25(2):404–414.
89. Nieves JW, Cosman F, McMahon D, et al. Teriparatide and pelvic fracture healing: a phase 2 randomized controlled trial. *Osteoporos Int.* 2022;33(1):239–250.
90. Bhandari M, Schemitsch EH, Karachalios T, et al. Romosozumab in skeletally mature adults with a fresh unilateral tibial diaphyseal fracture: a randomized phase-2 study. *J Bone Joint Surg Am.* 2020;102(16):1416–1426.
91. Sim IW, Borromeo GL, Tsao C, et al. Teriparatide promotes bone healing in medication-related osteonecrosis of the jaw: a placebo-controlled, randomized trial. *J Clin Oncol.* 2020;38(26):2971–2980.
92. Mastaglia SR, Aguilar G, Oliveri B. Teriparatide for the rapid resolution of delayed healing of atypical fractures associated with long-term bisphosphonate use. *Eur J Rheumatol.* 2016;3(2):87–90.

93. Kondo N, Miyasaka D, Watanabe Y, et al. Atypical femoral fracture associated with delayed union for which the cessation of alendronate and daily administration of teriparatide contributed to fracture healing: histopathological evidence of the enhancement in bone formation parameters. *Mod Rheumatol Case Rep.* 2020;4(1):141–146.
94. Dos Santos Ferreira L, Abreu LG, Calderipe CB, et al. Is teriparatide therapy effective for medication-related osteonecrosis of the jaw? a systematic review and meta-analysis. *Osteoporos Int.* 2021;32(12):2449–2459.
95. Anabtawi M, Tweedale H, Mahmood H. The role, efficacy and outcome measures for teriparatide use in the management of medication-related osteonecrosis of the jaw. *Int J Oral Maxillofac Surg.* 2021;50(4):501–510.
96. van de Laarschot DM, McKenna MJ, Abrahamsen B, et al. Medical management of patients after atypical femur fractures: a systematic review and recommendations from the European Calcified Tissue Society. *J Clin Endocrinol Metab.* 2020;105(5):1682–1699.
97. Buerba RA, Sharma A, Ziino C, et al. Bisphosphonate and teriparatide use in thoracolumbar spinal fusion: a systematic review and meta-analysis of comparative studies. *Spine (Phila Pa 1976).* 2018;43(17):E1014–E23.
98. Fatima N, Massaad E, Hadzipasic M, et al. Assessment of the efficacy of teriparatide treatment for osteoporosis on lumbar fusion surgery outcomes: a systematic review and meta-analysis. *Neurosurg Rev.* 2021;44(3):1357–1370.