REVIEW ARTICLE

Newer Therapies for Osteoporosis: A Systematic Review

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Abstract

Objective: The current management of osteoporosis has several unmet needs. Consequently, the newer and upcoming agents and targets are being expectantly looked at. We aim to appraise the evidence examining the efficacy of the newer therapies for the management of osteoporosis.

Methods: Scopus, Embase, and MEDLINE databases were screened from January 2013 to December 2023 to identify clinical trials that evaluated the efficacy of newer agents for the treatment of osteoporosis in men and postmenopausal women (PMO). Changes in bone mineral density (BMD) and incidences of vertebral fractures (VFs) and nonvertebral fractures (NVFs) or relative risk reduction (RRR) for VF and NVF were retrieved. The Oxford quality scoring system was applied to evaluate the methodological quality of the included clinical trials.

Results: Eighteen randomized controlled trials (RCTs) that had enrolled 22,868 PMO and 473 male participants were included. Anabolic agents abaloparatide and romosozumab exhibited significant BMD gain and relative RRR for fractures and greater efficacy than teriparatide. Blosozumab was reported to exhibit substantial BMD gains. The efficacy of a sequential therapeutic strategy with anabolic agent followed by antiresorptive agents was superior to the reverse sequence.

Conclusion: Newer therapies for osteoporosis exhibited significant BMD gain and fracture risk reduction in men and PMO. The newer anabolic agents demonstrated greater efficacy than any of the previously available therapeutic options.

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Introduction

Osteoporosis-related fractures are one of the leading causes of chronic disease morbidity following ischemic heart disease, dementia, and lung cancer.[1] The economic burden, morbidity, and mortality associated with fragility fractures are substantial and likely to rise in the future in the aging population.[2] Epidemiological studies have observed a robust concurrence between treatment-induced bone mineral density (BMD) accrual and fracture risk reduction. However, there is limited evidence examining the protracted efficacy and safety of the newer therapies for osteoporosis. It is, therefore, imperative that the next-generation antiosteoporosis drugs treat osteoporosis with sufficient antifracture efficacy and with minimal toxicity. Insights from basic bone pathophysiology have recognized several new therapeutic targets for the management of osteoporosis (Table 1). The objective of this systematic review was to study the evidence related to the efficacy of the newer therapies for osteoporosis.

Methods

This systematic literature review has been reported in accordance with the recommendations of the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines 2020[3] (Supplementary material).

Data Sources and Search Strategies

A thorough bibliographic search was performed in the Scopus, MEDLINE, and Embase databases to identify randomized controlled trials (RCTs) (either placebo or active-controlled) published between January 2013 and December 2023 that evaluated the efficacy of newer osteoporotic agents among postmenopausal women (PMO) and men with primary osteoporosis. A combination of appropriate Medical Subject Headings (MeSH) terms and keywords was used (Supplementary material). References were also manually searched among previously published reviews. The clinical trial registry (www.clinicaltrial.gov) was searched for any potential unpublished studies.

Study Selection

The selection criteria for this systematic review were framed using the PICO format: P (population): PMO or men with primary osteoporosis (i.e., age-related osteoporosis); I (intervention): newer therapies for osteoporosis; C (comparison): placebo or other active drugs; O (outcome): (1) evolution of BMD at lumbar spine (LS), total hip (TH), femoral neck (FN), (2) incidence of vertebral fracture (VF) and nonvertebral fracture (NVF) or RRR of VFs or NVFs (Table 2).

Studies published in non-English languages, those discussing secondary causes of osteoporosis, case reports or series, letters to the editor, review articles, pooled data analyses, and conference abstracts were excluded.

Data Extraction

Studies were obtained by two reviewers (DR, PD) using standardized data extraction strategies and were transferred to an Excel spreadsheet. The third and fourth reviewers (MG, VR) reviewed the extracted data. The following categories were considered for data extraction: study protocol (sample size, groups, and intervention), treatment (dosage, type of drugs, and route of administration), and clinical outcome (densitometric evaluation of the evolution of BMD, incidence of fracture). Finally, these studies were assessed independently by all four reviewers (PD, MG, DR, and VR), and a consensus settled disagreements.

The following outcome measures were extracted and tabulated: (1) evolution of BMD at LS, TH, and FN and (2) incidences of VF and NVF or RRR for VF or NVF. The evolution of BMD was defined as a difference in the percentage of BMD change between the intervention groups from the start to the completion of the study. There were wide variations in the reporting patterns and methodology used in these published trials. The respective authors of individual studies were contacted in case of incomplete data availability.

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Table 1: Potential therapeutic targets

Pathways	*Groups*	*Drugs*
Antiresorptive drugs		
RANKL/RANK/OPG pathway	RANKL inhibitor	Denosumab
Targeting the molecules of the Howship's lacuna	Cathepsin K inhibitor	Odanacatib Balicatib ONO-5334 MIV-711
	αvβ3 integrin antagonist	L-000845704 HSA-ARLDDL M-CSFRGD
	Chloride channel-7 inhibitor	N53736
	C-src kinase inhibitors	
Selective estrogen receptor modulators (SERMs)		Arzoxifene Lasofoxifene Bazedoxifene
Anabolic drugs		
	Parathyroid hormone receptor agonist	Teriparatide Abaloparatide
WNT signaling antagonists	Sclerostin neutralizing antibodies	Romosozumab Blosozumab
	DKK-1 inhibitors	
	Calcium-sensing receptor antagonism	
	Activin inhibitors	ACE-011
	Matrix extracellular phosphoglycoprotein (MEPE) fragments	

Table 2: Inclusion criteria

PICO(S) criteria	
Patient	Men and postmenopausal women with osteoporosis (i.e., age-related osteoporosis)
Intervention	Newer therapies for osteoporosis
Comparator	Placebo or other active osteoporosis agents
Outcome	Evolution of BMD at lumbar spine, total hip, and femoral neck Incidence of vertebral fractures and nonvertebral fractures
Study design	Placebo-controlled randomized controlled trials (RCTs) RCTs including other active osteoporosis agents Controlled clinical trials (CCTs) >100 participants

Assessment of Quality

The methodological quality of the selected studies was analyzed by the Oxford quality scoring system, assessing the randomization, blinding, statistical analysis, withdrawal, and dropout processes.[4]

Results

A total of 1,038 potentially relevant publications were retrieved. After excluding duplicates, 866 eligible manuscripts were considered for evaluation. Following a screening pertaining to relevant titles and abstracts, 172 articles underwent a full-text review. Finally, 18 RCTs (9 placebo and 9 active controlled) were incorporated in this systematic review that fulfilled the inclusion criteria. A flow diagram illustrating the literature search strategy is depicted in Figure 1.

In these 18 studies, 22,868 women with PMO and 473 men with low BMD were included. Fourteen out of the 18 included studies (i.e., 77.77%) were double-blinded. The detailed characteristics of the studies discussing the newer therapies for osteoporosis, that is, abaloparatide (ABL) (n = 5),[5–9] romosozumab (ROM) (n = 6),[10–15] and blosozumab,[16] have been shown in Table 3. In addition, the efficacy of sequential therapy with these newer agents was also evaluated (n = 6),[17–22] as given in Table 4. All RCTs scored 3–5 (out of 5) using methodological quality assessment with the Oxford quality scoring system, qualifying as high-quality trials. The median duration of intervention was 24 weeks (ranging from 12 to 84 weeks).

The primary outcome was LS BMD in 11 studies (61.11%). Relative risk reduction (RRR) was calculated in five studies (29.41%), whereas the incidences of VF and NVF were reported in a narrative in seven studies (38.88%). Available evidence has been discussed under the following subheadings.

Effect of Anabolic Agents on Bone Mineral Density

Abaloparatide

Abaloparatide, a novel synthetic peptide analog of the first 34 amino acids of the human parathyroid hormone-related peptide (PTHrP), received its Food and Drug Administration (FDA) approval in April 2017 for the management of PMO in women at high fracture risk and in patients intolerant to other osteoporosis drugs. Five RCTs[5–9] on ABL have observed significant BMD gain at the LS, TH, and FN and a robust antifracture efficacy. *Abaloparatide vs placebo:* Leder et al.,[5] ACTIVE Trial—Miller et al.,[6] and Matsumoto et al.[7] evaluated 2,854 women with PMO and observed significant improvement in LS, TH, and FN BMD in comparison to placebo (Table 3). ATOM study[8] studied the efficacy and safety of ABL in 228 men with osteoporosis and reported significant improvement in LS, TH, and FN BMD in comparison to placebo.
Abaloparatide vs teriparatide: In the ACTIVE trial,[6] 2,643 women with PMO were randomized to receive ABL, teriparatide, and placebo for 18 months. The percentage difference from baseline BMD at 18 months was slightly greater with ABL than with teriparatide at the LS, TH, and FN, suggesting ABL was a more effective therapeutic option.
Abaloparatide vs alendronate: No head-to-head trial comparing the efficacy of ABL and antiresorptive therapy is available. In a *post hoc* analysis, at the end of the 43-months of integrated ACTIVE–ACTIVExtend study,[6,20] women receiving ABL (18 months) followed alendronate (24 months) showed significant BMD gain at the LS, TH, and FN in comparison to treatment with placebo (18 months) followed by alendronate (24 months), suggesting ABL succeeded by alendronate as an attractive strategy for sequential therapy.

The common adverse reactions of ABL that are reported in clinical trials were nausea, headache, fatigue, palpitations, vertigo, and upper abdominal pain. Other adverse effects include orthostatic hypotension, hypercalcemia, and urolithiasis. The prevalence of hypercalcemia was lower in the ABL group by 51% vs teriparatide.[6]

Romosozumab

Romosozumab, a humanized monoclonal antibody to sclerostin, received its FDA approval in April 2019. ROM demonstrated a "dual effect" of augmentation of bone formation and suppression of bone resorption by blocking sclerostin.
Romosozumab vs placebo: McClung et al.,[10] FRAME study,[11] and Ishibashi et al.[12] evaluated 7,851 women with PMO and observed

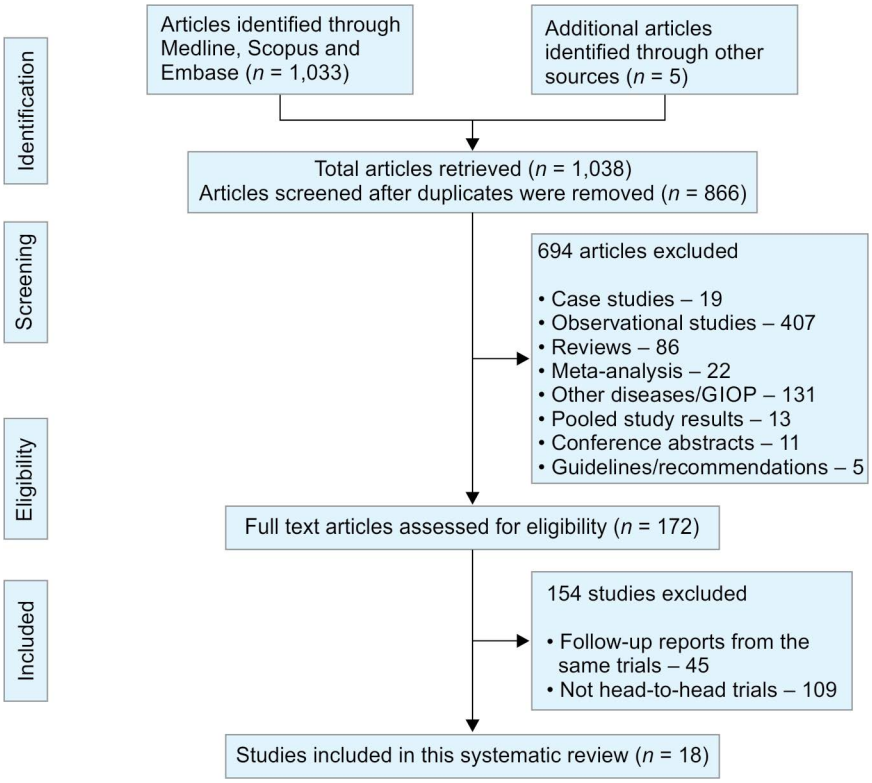

Fig. 1: Screening and selection process of studies on the newer therapies for osteoporosis

significant improvement in LS, TH, and FN BMD in comparison to placebo. BRIDGE study[13] examined the efficacy of ROM in 245 men with osteoporosis and demonstrated significant improvement in LS, TH, and FN BMD in the ROM group compared to placebo.

In the FRAME trial,[11] 7,180 women with PMO were randomized to receive ROM 210 mg subcutaneously (SC) or placebo once a month for 12 months, followed by denosumab 60 mg SC 6 monthly in both groups for a year, and reported significantly increased LS and TH BMD (13 and 7% respectively) compared to placebo.

Romosozumab vs alendronate: In the ARCH trial,[14] ROM (210 mg SC monthly) was compared with oral alendronate (70 mg weekly) for a year, followed by oral alendronate in both groups for 2 years, and a significantly higher BMD gain from baseline with ROM compared to alendronate after a year and further BMD gain following the transition to alendronate was observed. Although BMD gain with ROM in the ARCH trial was similar to that seen in the FRAME study[11] at 1 year, the observed BMD gain at 36 months was comparatively lower in the FRAME study.

Romosozumab vs teriparatide: In the STRUCTURE trial,[15] ROM (210 mg SC monthly) was compared with teriparatide (20 µg SC daily) for 12 months in women with PMO who had received oral bisphosphonates for at least 3–4 years and observed favorable BMD gain with ROM at LS (9.8 and 5.4%, respectively) and TH (2.6 and −0.6%, respectively), inferring that in patients transitioning from bisphosphonates to anabolic therapy, ROM may be more efficacious than teriparatide.

McClung et al.[10] compared five doses of ROM with teriparatide (20 µg SC daily), oral alendronate (70 mg weekly), and subcutaneous placebo, and observed BMD accrual at 12 months with ROM, teriparatide, and alendronate at LS was 11.3, 7.1, and 4.1%, respectively, and at TH was 4.1, 1.3, and 1.9%, respectively, confirming higher BMD gain at all skeletal sites with ROM.

The safety data analysis for ROM emerged from the FRAME and ARCH trials.[11,12] Major cardiovascular event (MACE) (composite of cardiovascular death, MI, and cerebrovascular events), hypocalcemia, osteonecrosis of the jaw, and atypical femoral fracture were higher with ROM in the ARCH and FRAME trials. A *post hoc* analysis demonstrated a higher incidence of MACE events in the ROM group (2%) when compared with the alendronate group (1.1%), with a hazard ratio of 1.7 (95% CI 1.1–2.6).[15] Further postmarketing surveillance studies are warranted to address these concerns.

Blosozumab

Blosozumab is a novel humanized monoclonal antibody against sclerostin. Evidence is accumulating confirming the role of blosozumab as a promising newer anabolic therapy for the management of osteoporosis. Recker et al.[16] evaluated 120 women with PMO and observed significant improvement in LS, TH, and FN BMD when in comparison to placebo. Fracture risk was not assessed.

Effect of Antiresorptive Agents on Bone Mineral Density

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) possess estrogen agonist or antagonist properties in different target tissues. Several newer generations of SERMs, for example, lasofoxifene and bazedoxifene (vide infra), have shown promising results on the BMD accrual, antifracture efficacy, and reduction in breast cancer risk. In two RCTs, the OPAL trial[23] and the PEARL trial,[24] lasofoxifene demonstrated a favorable impact on BMD, whereas only the PEARL trial exhibited diminished risks of vertebral and NVFs.

Cathepsin K Inhibitors

Odnacatib, balicatib, and ONO-5344 are inhibitors of cathepsin K. They have all been withdrawn from the market or had further development discontinued (vide infra).

Newer Agents that have been Discontinued

Bazedoxifene

Bazedoxifene, a third-generation SERM, is primarily used for the treatment of women with PMO.

Bazedoxifene vs placebo: Palacios et al.,[25,26] Beck et al.,[27] and Pinkerton et al.[28] evaluated 10,511 women with PMO and observed significant improvement in LS BMD when compared with placebo (Table 4). However, Palacios et al.[25] observed a smaller decrease in TH BMD in the bazedoxifene 20 mg (–1.19%) and 40 mg (–1.15%) groups in comparison to the placebo group (–2.53%; $p \leq 0.002$) following 7 years of therapy. Bazedoxifene has been withdrawn from sale in 2020 because of commercial reasons and is awaiting a relaunch with improved packaging.

Odanacatib

Odanacatib is a cathepsin K inhibitor. Several RCTs demonstrated the favorable efficacy of odanacatib at LS, TH, and FN and a substantial antifracture efficacy when compared with placebo.[29–35] However, a safety analysis perceived a significant increment in the risk of stroke, and odanacatib was, therefore, withdrawn from further development.

Table 3: Clinical trials assessing the efficacy of the newer anabolic agents on osteoporosis

	Study design	*Country*	*Number of patients/group*	*Treatment*	*Comparator*	*Length of intervention*	*Outcomes*	*Fracture risk reduction (RRR)*	*Oxford quality scoring system*	*FDA approval*
Abaloparatide										
Leder et al.[5]	Double-blind placebo-controlled RCT	Multicenter, multinational (United States, Argentina, India, and the United Kingdom)	222 women with postmenopausal osteoporosis	Abaloparatide (ABL): G1: 20 µg: (n = 43), G2: 40 µg: (n = 43), G3: 80 µg: (n = 45)	Teriparatide (TPT), 20 µg: (n = 45) orplacebo (PBO): (n = 45)	24 weeks,	Percentage change from baseline BMD at 24 weeks: LS ABL—2.9% (20 µg), 5.2% (40 µg), and 6.7% (80 µg); TPT—5.5%; PBO: 1.6% TH ABL—1.4% (20 µg), 2% (40 µg), and 2.6% (80 µg); TPT—0.5%; PBO: 0.4% FN ABL—2.7% (20 µg), 2.2% (40 µg), and 3.1% (80 µg); TPT—1.1%; PBO: 0.8%	RRR not calculated	3	FDA approved
Miller et al.[6]	Phase III double-blind placebo-controlled RCT	28 study centers in 10 countries	2,463 women with postmenopausal osteoporosis	Subcutaneous ABL: (n = 824)	Teriparatide: 818;PBO: (n = 821)	18 months	Percentage change from baseline BMD at 18 months: LS—(11.20 vs 10.49 vs 0.63%) TH—(4.18 vs 3.26 vs −0.10%) FN—(3.60 vs 2.66 vs −0.43%)	New morphometric vertebral fractures occurred ABL = 4 PBO = 30 [risk difference (RD) vs placebo, −3.64 (95% CI: −5.42 to −2.10); relative risk, 0.14 (95% CI: 0.05–0.39); p <.001] TPT = 6 [RD vs placebo, −3.38 (95% CI: −5.18 to −1.80); relative risk, 0.20 (95% CI: 0.08–0.47); p < 0.001]	5	
Matsumoto et al.[7]	Phase II, double-blind, placebo-controlled RCT	Japan	164 women with postmenopausal osteoporosis	ABL 40 µg (n = 55) or ABL 80 µg (n = 54)	PBO (n = 55)	48 months	Percentage change from baseline at 48 weeks: LS: ABL 40 µg vs PBO—6.6% [95% confidence interval (CI) 4.70–8.54; p < 0.001] ABL 80 µg vs PBO—11.5% (95% CI 9.59–13.45; p < 0.001) ABL 80 µg vs ABL 40 µg—4.9% (95% CI 2.98–6.83; p < 0.001) TH: PBO—0.4 ± 1.9%; ABL 40 µg—1.5 ± 2.2% (95% CI: 0.22–1.94 vs PBO) ABL 80 µg—2.9 ± 2.2% (95% CI: 1.61–3.35 vs PBO) and 0.51–2.30 vs ABL 40 µg FN: PBO—0.9 ± 3.0%, ABL 40 µg vs PBO—1.5 ± 2.5% (95% CI: 0.54–1.75) and ABL 80 µg—2.3 ± 3.3% (95% CI: 0.14–2.78 vs PBO and 0.33–2.05 vs ABL 40 µg)	RRR not calculated	5	
ATOM study (Czerwinski et al.[8])	Phase III double-blind placebo-controlled RCT	United States	228 men with osteoporosis	Abaloparatide (ABL): (n = 149)	Placebo: (n = 79)	12 months	Percentages change in BMD from baseline in lumbar LS, TH, and FN at 12 months were 8.48, 2.14, and 2.98% with ABL compared with PBO 1.17% (p < 0.0001)	ABL: 1 PBO: 3	4	
Lewiecki et al.[9]	Phase III, randomized, open-label, multicenter, noninferiority study	United States	511 women with postmenopausal osteoporosis	Abaloparatide-subcutaneous injection (ABL-SC) (n = 255)	ABL-microstructure transdermal system (ABL-sMTS) (n = 256)	12 months	The least significant percent change from baseline in LS BMD at 12 months was 7.14% (SE: 0.46%) for ABL-sMTS and 10.86% (SE: 0.48%) in the ABL-SC group	ABL-sMTS: 8 ABL-SC, 11	5	

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	Study design	*Country*	*Number of patients/group*	*Treatment*	*Comparator*	*Length of intervention*	*Outcomes*	*Fracture risk reduction (RRR)*	*Oxford quality scoring system*	*FDA approval*
Romosozumab										
McClung et al.[10]	Phase II, multicenter, international, placebo-controlled RCT	International, multicenter study	419 women with postmenopausal osteoporosis	5 groups of romosozumab (ROMO): G1: 70 mg, monthly G2: 140 mg, monthly G3: 210 mg, monthly G4:140 mg, every 3 months G5: 210 mg, every 3 months	Subcutaneous PBO ororal alendronate (ALN) (70 mg weekly) orsubcutaneous teriparatide (TPT) (20 µg daily)	12 months	Percentage change from baseline BMD at 12 months Largest in ROMO 210 mg monthly: LS: 11.3%, TH: 4.1%, FN: 3.7% TPT—LS: 7.1%, TH: 1.3%, FN: 1.1% ALN—LS: 4.1%, TH:1.9%, FN: 1.2%	RRR not calculated	5	FDA approved
FRAME (Cosman et al.[11])	Phase III, international, placebo-controlled, double-blind, RCT	Multicenter, multinational	7,180 women with postmenopausal osteoporosis	Romosozumab (ROMO), 210 mg subcutaneously every month;(ROMO): *N* = 3,589	Placebo (PBO): 3,591	12 months	Percentage change from baseline BMD in 12 months: LS:96 to ≥3%, 89 to ≥6%, and 68% to ≥10%, compared with 22, 6, and 1% with PBO TH:78 to ≥3%, 47 to ≥6%, and 16 to ≥10%, compared with 16, 3, and 0% with PBO	With ROMO,RRRs of fracture were81% for vertebral fractures, 32% for clinical fractures, 25% for nonvertebral fractures, 55% for hip fractures, 39% for major osteoporotic fractures, and 32% for major nonvertebral fractures	5	
Ishibashi et al.[12]	Phase II, multicenter, placebo-controlled RCT	Japan	252 women with postmenopausal osteoporosis	G1: ROMO 70 mg QM: 63 G2: ROMO 140 mg QM: 63; and G3: ROMO 210 mg QM: 63	Placebo (PBO): 63	12 months	Percentage change from baseline BMD at 12 months: LS: 0.9% in the PBO and 8.4, 13.3, and 16.9% in the ROMO 70, 140, and 210 mg QM groups (all $p < 0.001$ vs PBO) TH/FN–largest gain (ROM: 210 mg) vs PBO ($p < 0.001$ for all)	RRR not calculated	5	
BRIDGE (Lewiecki et al.[13])		Multicenter, multinational	245 men with osteoporosis	Romosozumab (*n* = 163)	Placebo (*n* = 82)	12 months	Percentage change from baseline BMD at 12 months: LS (12.1 vs 1.2%; $p < 0.001$) TH (2.5 vs 20.5%; $p < 0.001$) FN (2.2 vs 20.2%; $p < 0.001$)	RRR not calculated	5	
ARCH (Saag et al.[14])	Phase III, multicenter, international, double-blind RCT	Multicenter, multinational	4,093 women with postmenopausal osteoporosis and a fragility fracture	Compared the cumulative incidence of new fractures between the romosozumab-to-alendronate (ROMO-ALN) group (*n* = 2,046) and the alendronate-to-alendronate (ALN-ALN) group	Alendronate (ALN): (*n* = 2,047)	24 months	Percentage change from baseline BMD in 24 months: LS—ROM-ALN: 15.2%; ALN-ALN: 7.1% TH—ROM-ALN: 7.1%; ALN-ALN: 3.4% FN—ROMO-ALN: 5.9%; ALN-ALN: 2.2%	ROMO-to-ALN group: 48% lower risk of new vertebral fractures than ALN alone (RR: 0.52) 38% lower risk of hip fracture, $p = 0.02$ 19% lower risk of nonvertebral fracture, $p = 0.04$	5	
STRUCTURE (Langdahl et al.[15])	Phase IIIb, randomized, open-label, active-controlled, parallel-group trial	Multicenter, multinational	436 women with postmenopausal osteoporosis transitioning from bisphosphonate therapy	Romosozumab (ROMO) (*n* = 218)	Teriparatide (TPT): (*n* = 218)	12 months	Percentage change from baseline BMD at 12 months: LS—ROM: 9.8%; TPT: 5.4% TH—ROM: 2·6% (95% CI: 2·2–3·0);TPT: 0·6% (–1·0 to –0·2) FN—ROMO: 3.2; TPT: –0.2%	ROMO: 8 (3%) TPT: 7 (4%)	3	
Blosozumab										
Recker et al. (2015)[16]	Phase II, double-blind placebo-controlled RCT	Multicenter, multinational (United States and Japan)	120 women with postmenopausal osteoporosis	Blosozumab: G1: 180 mg every 4 weeks (Q4W): (*n* = 31) G2: 180 mg every 2 weeks (Q2W): (*n* = 30),and G3: 270 mg every 2 weeks (Q2W): (*n* = 30)	Placebo (*n* = 29)	52 weeks	Percentage change from baseline BMD in 52 weeks: LS: G1: 180 mg Q4W 8.4% G2: 180 mg Q2W –14.9% G3: 270 mg Q2W –17.7% TH: G1: 180 mg Q4W –2.1% G2: 180 mg Q2W –4.5% G3: 270 mg Q2W –6.7% FN: G1: 180 mg Q4W –2.7% G2: 180 mg Q2W –3.9% G3: 270 mg Q2W –6.3%	RRR not calculated	5	Not approved

Table 4: Clinical trial assessing the efficacy of sequential therapy with newer therapies for osteoporosis

Author	*Study design*	*Country*	*Number of patients/ group*	*Treatment*	*Comparator*	*Length of intervention (months)*	*Outcomes*	*Fracture risk reduction*	*Oxford quality scoring system*
VICTOR study (Kobayakawa et al.[17])	Multicenter, RCT	Japan	294 women with postmenopausal osteoporosis with severe risk of fracture	12 months of ROM followed by either ibandronate (IBA)/DMab for an additional 12 months	124 patients (62 each in IBA and DMab group)	24	Mean changes in BMD in the sequential phase: LS: 2.5 ± 0.8% IBA 5.4 ± 0.8% iDMAb TH: 2.5 ± 0.8% IBA 4.0 ± 0.9% DMab FN: 2.7 ± 0.8% IBA 3.1 ± 0.8% DMab	No new fractures in IBA 1 (1.6%) new vertebral fracture in a DMab patient	3
McClung et al.[18]	Phase II, dose-finding RCT	Multicenter, multinational (United States, Australia, Saudi Arabia, Belgium, Denmark, Canada)	141 women with low BMD	Randomized to DENO (60 mg SC Q6M) or PBO for 12 months Followed by open-label ROMO (210 mg QM) for 12 months At month 48: if on active treatment for 48 months further active treatment All other subjects: Zoledronate (ZOL) 5 mg IV *N* = 51 in no further active treatment *N* = 90 in ZOL group	Within groups	72	Mean BMD t-score LS No further active t/t group Baseline (month 0): –2.32 Month 48: –1.04 ZOL 5 mg IV single dose group; Baseline (month 0): –2.34 Month 48: 1.28 TH: No further active t/t group Baseline (month 0): –1.63 Month 48: –1.29 ZOL 5 mg IV single dose group Baseline (month 0): –1.42 Month 48: –1.16 FN: No further active t/t group Baseline (month 0): –1.98 Month 48: –1.70 ZOL 5 mg IV single-dose group Baseline (month 0): –1.86 Month 48: –1.63	RRR not calculated. No further active treatment group: 1 radius and 1 fibula fracture ZOL group: 1 radius and 1 rib fracture	5
McClung et al.[19]	Phase II RCT	Multicenter, multinational (United States, Australia, Saudi Arabia, Belgium, Denmark, Canada)	28 women with postmenopausal osteoporosis	Group 1: PBO (24 months) to PBO (12 months) to ROMO (12 months) (*n* =12) Group 2: PBO (24 months) to DENO (12 months) to ROMO (12 months) (*n* = 16)	PBO	48	Increase in BMD with romosozumab Group 1: PBO to PBO to ROMO LS: 9.1% TH: 4.6% FN: 3.9% Group 2: PBO to DENO to ROMO LS: 11.5% TH: 3.8% FN: 3.2%	RRR not calculated	5

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Author	*Study design*	*Country*	*Number of patients/ group*	*Treatment*	*Comparator*	*Length of intervention (months)*	*Outcomes*	*Fracture risk reduction*	*Oxford quality scoring system*
ACTIVExtend trial (Bone et al.[20])	Phase III RCT	Multicentric	558 women with postmenopausal osteoporosis from ACTIVE's ABL group and 581 from PBO group	Women who completed ABL or PBO in ACTIVE trial were eligible to receive up to 24 months of ALN	PBO	43	Mean absolute increases in BMD from ACTIVExtend baseline to ACTIVExtend month 24 LS: ABL/ALN: 0.0265 PBO/ALN: 0.0479 TH: ABL/ALN: 0.0166 PBO/ALN: 0.0210 FN: ABL/ALN: 0.0114 PBO/ALN: 0.0143	New radiographic vertebral fracture ABL/ALN group: 0.9% PBO/ALN: 5.6% RRR: 84% RRR for ACTIVExtend only for vertebral fractures for ABL/ALN vs PBO/ALN: 87% Hip fractures: 0 in ABL/ALN 5 in PBO/ALN	5
McClung et al.[21]	Phase II RCT	Multicenter, multinational (Australia, Canada, Spain, Belgium, Australia, United States, Argentina, United Kingdom)	364 women with postmenopausal osteoporosis	ROMO: 70, 140, and 210 mg monthly (QM); 140 mg Q3M; 210 mg Q3M) for 24 months or PBO for 24 months or open-label alendronate (ALN) for 12 months followed by ROMO 140 mg QM for 12 months	Rerandomized 1:1 within the original treatment groups to PBO or denosumab (DMab) 60 mg Q6M for another 12 months	36	Gain in BMD at months 12 and 24: ROMO 210 mg QM: LS: 11.3, 15.1% TH: 4.1, 3.7% FN: 5.4%, 5.2% Other ROMO treatment groups: (all $p \leq 0.01$ vs PBO) ALN to ROMO 140 mg QM: LS: 4, 9% TH: 1.9, 2.6% FN: 1.3, 2.6% ROMO 210 mg QM for 24 months-DMab during extension (till month 36): LS: 2.6% TH: 1.9% FN: 1.4%	Incidence of fragility fractures from months 24 to 36: 5 (3.9%) PBO 4 (3.2%) DMab ROMO to PBO: no vertebral fractures ROMO to DMab: two vertebral fractures	5
FRAME EXTENSION (Lewiecki et al.[22])	Phase III RCT	Multicenter, multinational	5,743 women with postmenopausal osteoporosis (2,851 ROMO-DENO; 2892 PBO-DENO)	Blinded ROMO (s.c) 210 mg or PBO once, monthly—12 months, followed by open-label denosumab (DMab) (s.c) 60 mg every 6 months for 12 months, f/b open-label DMab (s.c) 60 mg every 6 months for a further 12 months (total 36 months)	PBO	36	Differences in relative increases from baseline in BMD ROMO-DMab vs PBO-DMab at 36 months LS: 10.5% TH: 5.2% FN: 4.8%	RRR in the first 12 months ROMO to DMab vs PBO to DMab Vertebral: 66% Clinical: 27% Nonvertebral: 21% Hip: 41% RRR of new vertebral fractures through 24 and 36 months Month 24: 75% Month 36: 66%	5

Balicatib

Balicatib is an emerging cathepsin K inhibitor. In a phase II RCT, 675 women with PMO were treated with four treatment arms of balicatib or placebo over 12 months and showed significantly increased LS BMD (upto 4.46%) and TH BMD when compared with placebo (0.25%).[36] Balicatib was, however, discontinued due to the development of morphea-like skin lesions.

ONO-5334

ONO-5334 is an oral cathepsin K inhibitor. In the OCEAN trial,[37] 285 women with low BMD or PMO with one fragility fracture were randomized to receive five treatment arms of ONO-5334, alendronate (70 mg once weekly), or placebo for 12 months. Patients receiving all doses of ONO-5334 and alendronate exhibited a significant increase in LS, TH (except ONO-5334, 100 mg once daily), and FN BMD, suggesting a potential target for treating osteoporosis. RRR was not calculated. There were no safety concerns. ONO-5334 also exhibited significant gain vs placebo for cortical, trabecular, and integral BMD at the LS and TH ($p < 0.001$).[38] ONO-5334 was withdrawn from the market for competitive reasons.

Effect on Fractures

The ACTIVE trial[6] reported four new morphometric VF occurring in the ABL group, whereas 30 of those occurred in the placebo group, with an RRR of 0.14 (95% CI: 0.05–0.39); ACTIVE–ACTIVExtend study[6,20] observed RRR for all clinical fractures (34%), VF (84%), NVF (39%), and major osteoporotic fractures (MOFs) (50%) in the ABL–alendronate group in comparison to the placebo–alendronate group. ABL has also been proven to be more efficacious than teriparatide with the NNT data analysis for clinical (37 for ABL vs 59 for teriparatide), VF (28 for ABL vs 30 for teriparatide), NVF (55 for ABL vs 92 for teriparatide), and MOF (34 for ABL vs 75 for teriparatide).[39]

In the FRAME trial, the ROM–denosumab group demonstrated 81% RRR for VF, 32% RRR for clinical fractures, 25% RRR for NVF, 55% RRR for hip fractures, and 39% RRR for MOF.[11] The ARCH study also reported a 48% RRR for new VF and 19% RRR for NVF, respectively, in the ROM–alendronate group in comparison to the alendronate–alendronate group.[12]

Palacios et al.[26] reported a considerable reduction of cumulative incidences of new VF and NVF after 7 years of therapy with bazedoxifene when compared with placebo (Table 4).

Sequential Therapy

In the aging population with osteoporosis, plural drugs are often needed to optimize the treatment-related fracture risk reduction, either as a sequence or in combination. The ACTIVE–ACTIVExtend analysis[6,20] showed that the participants in the ABL–alendronate group had favorable BMD accrual at the LS, TH, and FN and better antifracture efficacy when compared with the placebo–alendronate group.

The VICTOR study[17] evaluated the efficacy of denosumab or ibandronate as a sequential therapeutic strategy following ROM therapy for 1 year, where denosumab was found to be more efficacious than ibandronate. It was observed that inceptive treatment with ROM for 1 year produced large BMD gains at the LS and TH, and subsequent transition to robust antiresorptive agents (alendronate or denosumab) resulted in augmentation of the BMD at skeletal sites.[18,19,21,22] Following 2 years of therapy, significant BMD gains were observed at the LS and FN when ROM was sequenced with denosumab or alendronate. However, BMD gain following a 2-year therapy with denosumab transitioning to ROM was reported to be comparably poorer, with a differential effect on hip BMD. ROM also effectively increased LS and TH BMD when used following alendronate therapy. It could, therefore, be concluded that BMD gains are larger with anabolic followed by antiresorptive compared to the reverse sequence.

Other Potential Targets

Anabolic Agents

Calcilytics (calcium-sensing receptor antagonists): Ronacalcet is a calcium-sensing receptor antagonist that promotes bone formation by stimulating endogenous PTH release. Fitzpatrick et al.[40] demonstrated modest gain in BMD at LS at 12 months with ronacalcet (0.3–1.6%), teriparatide (9.1%), or alendronate (4.5%), but exhibited a decrease in TH and FN BMD with ronacalcet as opposed to an increase in teriparatide and alendronate arms. ATF936, a novel oral calcilytic, showed encouraging results in animal models.[41]

Dickkopf-1 inhibiton: Dickkopf-1 (Dkk-1), an inhibitor of the WNT/β-catenin signaling pathway, acts by forming a ternary complex with Kremen and LRP5/6. Treatment with anti-Dkk-1 monoclonal antibody exhibited enhanced BMD in ovariectomized monkeys[42] and is under development as a potential anabolic agent.

Matrix extracellular phosphoglycoprotein fragments: Matrix extracellular phosphoglycoprotein (MEPE) fragments are SIBLING (small integrin-binding ligand N-linked glycoproteins) proteins that are usually expressed in differentiated osteoblasts and osteocytes and play an essential role in phosphate regulation and osteogenesis. Although preclinical studies demonstrated new bone formation and fracture healing,[43] further studies are warranted to establish their efficacy as skeletal anabolic agents.

Endocannabinoids: It is well-recognized that the skeletal endocannabinoid system and its receptors play a crucial role in the regulation of BMD and bone turnover. Hanus et al.[44] demonstrated that CP-55,940 (a nonselective cannabinoid receptor agonist) and HU 308 (a cannabinoid CB 2 selective agonist) have facilitated early maturation of bone marrow derived osteoblast precursors and enhancement of BMD.

Activin-follistatin-inhibin hormonal system: Bone metabolism is perceived to be influenced by the activin-follistatin-inhibin (AFI) hormonal system. Activin inhibits bone formation and stimulates bone resorption. Follistatin-inhibin and other proteins antagonize and downregulate activin signaling. Fajardo et al.[45] reported that ACE-011 has dual antiresorptive and anabolic effects on the skeletal system and a marked increment in BMD and bone strength in animal studies.

Stem cell therapy: Mesenchymal stem cells (MSCs) differentiate and evolve into osteoblasts under the influence of various cytokines, growth factors, for example, transforming growth factor beta (TGFβ), fibroblast growth factor (FGF), insulin-like growth factor 1 (IGF 1), bone morphogenetic protein (BMP), Wnt, and hormones such as parathyroid hormone,[46] whereas hematopoietic stem cells differentiate to osteoclasts *via* stimulation of NF-κB ligand (RANKL), receptor activation of monocyte/macrophage colony-stimulating factor.[47] Following transplantation, MSCs display their anabolic effect either by differentiating into osteoblasts or by their paracrine effects through the secretion of growth factors and recruitment of reparative cells.[48] Interestingly, MSCs can escape allogeneic rejection by creating an immunosuppressive locus and being hypoimmunogenic.[49] Genetically modified MSCs such as biomaterial scaffolds in combination with gene delivery systems for PDGF-B and BMP-7 expression have demonstrated better long-term engraftment outcomes.[50,51] López-Delgado et al.[52] evaluated *in vivo* bone health in 103 stem cell implant recipients (47 patients with osteoporosis, 56 patients with osteoarthritis) and observed new bone formation in 45% of the recipients

with osteoporosis cells and 46% of those with osteoarthritis cells.

Antiresorptive Agents

αVβ3 integrin antagonists: Integrins such as $\alpha_V\beta_3$ integrin receptors are transmembrane receptors that facilitate the binding of osteoclasts with bone matrix proteins. The $\alpha_V\beta_3$ integrin crosstalks with extracellular matrix proteins containing the arginine–glycine–aspartic acid amino acid sequences, and destruction of this linkage hinders osteoclast adhesion. In a phase II trial, L-000845704, an $\alpha_V\beta_3$ integrin receptor antagonist, showed significant enhancement of LS BMD by 3.5% and a decrease in bone turnover markers by 40%, advocating L-000845704 as a promising drug for osteoporosis.[53]

Chloride channel inhibitors: Chloride channel activity plays a crucial role in the maintenance of an acidic milieu within the sealing zone of osteoclasts. ClC-7, a member of the voltage-gated chloride channels family, is found in the ruffled membrane and lysosomes of osteoclasts. Schaller et al.[54] reported that NS3736, a ClCN7 inhibitor, inhibits bone decay in ovariectomized rats, resulting in net BMD gain.

Discussion

This systematic review has appraised the current evidence exploring the efficacy of newer therapies for osteoporosis such as ABL, ROM, bazedoxifene, and ONO-5334.

Abaloparatide, in several RCTs, has exhibited substantial BMD gain at LS, TH, and FN[5–9,25] and a substantial reduction in VF, NVF, clinical, and MOF[6,20] compared to the placebo group. However, there is growing evidence to suggest that BMD accrual from ABL to teriparatide may dissipate soon after treatment withdrawal,[55] but more certainty of evidence is warranted to advocate judicious use of sequential therapy with robust antiresorptive agents to preserve the BMD gain.

Following a year of treatment with ROM, the BMD gain at LS in FRAME,[11] ARCH,[14] and Ishibashi et al.[12] was 13.7, 13.1, and 16.9%, TH was 6.2, 6.0, and 4.7%, respectively. When ROM was prescribed for 1 year following an antiresorptive therapy such as denosumab[56] or alendronate (STRUCTURE), BMD gain in LS was 9.8 and 5.3% and TH 2.9 and 0.9%, respectively, which was less favorable compared to treatment-naïve patients. These results are consistent with a multicenter, prospective, and observational study including 130 treatment-naïve patients receiving ROM for 12 months.[57] Over 2 years, sequential therapy with ROM followed by denosumab demonstrated better BMD gain at LS and TH (ROM-denosumab group 16.6 and 8.5%, respectively) compared with alendronate (ROM–alendronate group 15.2 and 7.1%) and (denosumab–ROM group 11.5 and 3.8%). This justifies the clinical use of anabolic followed by antiresorptive therapy, especially in severe osteoporosis and elevated risk of fractures. Keaveny et al.[58] demonstrated a better anabolic effect at the LS with ROM at 1 year, both at the trabecular and cortical bone compartments, when compared to teriparatide (27.3 vs 18.5%; $p = 0.005$) and placebo (27.3 vs –3.9%; $p < 0.0001$).

The evidence surrounding optimum approaches for sequential and combination therapy with conventional and newer therapies for osteoporosis remains unclear. DATA-SWITCH study reported the largest BMD gain at the LS, TH, and wrist in women treated with combined teriparatide–denosumab therapy for 2 years, followed by denosumab monotherapy for 2 years, compared to teriparatide for 2 years followed by denosumab for 2 years and denosumab for 2 years followed by teriparatide for 2 years.[59] Further structured studies are required to investigate the optimum sequential and combination therapy regimes that can be employed in clinical practice to improve skeletal integrity in osteoporosis.

There is a dearth of evidence exploring the association between sequential therapy and fracture outcomes. It was observed that fracture risk reduction of VF and NVF was more robust with anabolic agents compared with antiresorptive agents in PMO and men, and the results were independent of baseline risk indicators. Several RCTs have demonstrated the antifracture efficacy of ABL and ROM. Bazedoxifene also exhibited efficacy for all fracture outcomes.[25,26]

The major strength of this systematic review is the robust methodology as per PRISMA guidelines. We used a comprehensive search strategy to minimize publication bias and included methodologically robust 18 RCTs assessing the efficacy of newer agents on BMD gain and fracture risk reduction among men and PMO with osteoporosis.

However, there are a few limitations relevant to this systematic review. First, there was limited evidence measuring the efficacy of newer therapies for osteoporosis in men, and therefore, the level of evidence may be considered as poor. Second, we observed a wide variation in the duration of osteoporosis-related treatment in these studies. Despite having significantly improved BMD at LS, several studies failed to demonstrate significant BMD gain or antifracture efficacy at TH, which could partially be explained by the shorter duration of intervention. Third, only a handful of studies examined the antifracture efficacy of these newer agents, and therefore, further studies are warranted to validate the pharmacotherapy-related RRR of the VF, NVF, or MOF in clinical practice.

Conclusion

In this systematic review, we have identified and discussed newer therapies for osteoporosis that enhance BMD at all skeletal sites and reduce VF and NVF risk in both PMO and men with osteoporosis. We envisage that real-world data over time will provide more evidence for the efficacy of these novel therapies in terms of comparative effectiveness and antifracture efficacy in men, and to explore the optimal strategy for sequential or combination therapy in severe osteoporosis.

Supplementary Material

Supplementary files are available with author. Please connect with author for the Supplementary content.

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