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REVIEW

A systematic review and meta-analysis of efficacy and safety of Romosozumab in postmenopausal osteoporosis

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Abstract

The study was conducted to illustrate the effect of Romosozumab in postmenopausal osteoporosis patients. Romosozumab decreased the incidence of vertebral, nonvertebral, and clinical fractures significantly. In addition, decreased incidence of falls and increased bone mineral density at lumbar spine, total hip, and femoral neck was observed. Romosozumab is a monoclonal antibody that acts against the sclerostin pathway leading to enhanced bone formation and reduced bone resorption in patients with osteoporosis. Electronic search was performed on Medline (via PubMed), The Cochrane Central Register of Controlled Trials, and clinicaltrials.gov, till May 2020, for RCTs evaluating the effectiveness of Romosozumab in postmenopausal osteoporosis. RCTs evaluating the effect of Romosozumab on fractures and bone mineral density in postmenopausal osteoporosis patients. Meta-analysis was performed by Cochrane review manager 5 (RevMan) version 5.3. Cochrane risk of bias 2.0 tool and GRADE pro-GDT were applied for methodological quality and overall evidence quality, respectively. One hundred seventy-nine studies were screened, and 10 eligible studies were included in the analysis, with a total of 6137 patients in romosozumab group and 5732 patients in control group. Romosozumab significantly reduced the incidence of vertebral fractures [OR = 0.43 (95%CI = 0.35–0.52), High-quality evidence], nonvertebral fractures [OR = 0.78 (95%CI = 0.66–0.92), High quality], and clinical fractures [OR = 0.70 (95%CI = 0.60–0.82), High quality] at 24 months. Significant reduction in incidence risk of falls [OR = 0.87 (95%CI = 0.78–0.96), High quality] was observed with romosozumab. Bone mineral density was significantly increased in the romosozumab treated groups at lumbar spine [MD = 12.66 (95%CI = 12.66–12.67), High quality], total hip [MD = 5.69 (95%CI = 5.68 – 5.69), Moderate quality], and femoral neck [MD = 5.18 (95%CI = 5.18–5.19), Moderate quality] at 12 months. The total adverse events [RR = 0.98(95%CI = 0.96–1.01), Moderate quality] and serious adverse events [RR = 0.98(95%CI = 0.88–1.08), Moderate quality] with romosozumab were comparable to the control group. The current analysis with evidence on efficacy and safety of Romosozumab, authors opine to recommend the use of Romosozumab treatment for post-menopausal osteoporosis.

Systematic review registration: PROSPERO registration number: CRD42019112196

Keywords Romosozumab · Osteoporosis · Meta-analysis

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Introduction

Osteoporosis is a disease of bones resulting in increased fragility and change of microarchitecture [1]. It causes loss of bone mineral density (BMD) hence decreasing the bone strength and can ultimately lead to increased risk of fractures at various sites like hip, wrist, and vertebrae [2]. Osteoporosis as a disease has a significant impact on the burden of disease, health-care expenses, associated morbidity, and mortality [3, 4]. Fractures in osteoporosis are quite frequent in older women (> 55 years) and men (> 65 years), resulting in significant bone-associated morbidity, mortality, and hefty expenses associated with the management of health care [3, 5]. Women in their postmenopausal period of life have to deal with various symptoms because of lack of estrogens which is also attributed as a primary factor in bone mass reduction and deterioration of structural architecture leading to osteoporosis [6].

Sclerostin is an osteocyte-derived molecule that is encoded by the gene called SOST, has been found to regulate bone turnover by inhibiting osteoblastogenesis and bone formation by blocking the Wnt signaling pathways which play a crucial role in bone formation and morphogenesis [7–9]. Current treatment therapies approved for primary osteoporosis are the anti-bone resorptive drugs which include bisphosphonates (BPNs), RANK-ligand inhibitor, denosumab, anabolic agent teriparatide, and abaloparatide [10, 11]. Romosozumab (ROMO), an antisclerostin monoclonal antibody, has a twin effect of increasing the formation of bone and decreasing its resorption by blocking the sclerostin pathways [12, 13]. Literature search reveals clinical trials with romosozumab as a treatment option in osteoporosis have been found to be associated with increased bone mineral density (BMD) [12, 14–19]. The Endocrine Society came up with updated guidelines for treating postmenopausal osteoporosis with ROMO, selective estrogen receptor modulators, hormone replacement therapies, tibolone, calcitonin, calcium, and vitamin D [20]. The guideline update recommends that "women with severe postmenopausal osteoporosis and at very high risk of fracture (defined as T-score less than − 2.5 and a prior fracture) or with a history of multiple vertebral fractures should be given Romosozumab 210 mg monthly for up to one year to reduce the risk of vertebral, hip, and nonvertebral fractures and in women who have completed the course of ROMO, should be treated with antiresorptive therapies in order to maintain BMD gains and reduce future risk of fracture" [20]. The present study was conducted for systematic review and meta-analysis of the randomized controlled trials (RCTs) of ROMO as compared to the control group to illustrate the effect of ROMO on changes in BMD and assess the incidence of novel vertebral fractures in postmenopausal osteoporosis patients. In addition, we assess the effect of ROMO on incidence of falls.

Methods

Protocol and registration

The present systematic review was done as per the "PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)" statement. The protocol has been registered with "PROSPERO (International Prospective Register of Systematic Reviews)" database; protocol number as CRD42019112196.

Criteria for study inclusion

Only RCTs evaluating the role of Romosozumab in postmenopausal osteoporosis were included. All other types of studies including observational studies, review articles, and epidemiological studies were excluded.

Search strategy and study selection

An electronic literature search was conducted on 28th May 2020. Medline (via PubMed), The Cochrane Central Register of Controlled Trials, and clinicaltrials.gov were searched. A bibliographic search of published articles was also done. There was no language (English) or publication status restriction. The search strategy was constructed for databases using the following medical subject headings: "Osteoporosis", "RCT", "Romosozumab".

Duplicates articles were removed. The titles and abstracts were screened by two independent researchers for potential eligibility. After the initial segregation, full texts articles were assessed for eligibility by two authors. Any discrepancy with them was resolved with the help of the corresponding author.

Data extraction

Individual study data with regard to the study design, ROMO doses, and regimens, number of subjects in each group, fracture, BMD data, and safety outcomes were noted. All information was filled on a pre-structured form.

Study outcomes

The primary objective was to assess the decrease in the incidence of fractures. The secondary objectives were the change in bone mineral density (BMD), incidence of

falls, and safety outcomes which included total and serious adverse events.

Quality assessment of studies

Two authors independently (SS and SD) assessed the methodological quality of the RCTs by using the Cochrane Collaboration risk of bias 2 tool (ROB-2) [6] and assessed them as Low, High, or some concerns [21]. For the synthesis of figure plots for the risk of bias, Robvis (visualization tool) was used [22].

Assessment of publication bias was evaluated by funnel plot and Egger's regression test. For fractures, Egger's test was not applied as studies were fewer than five. So, publication bias was assessed for BMD, where a majority of the included studies reported the outcome.

Data synthesis and summary measures

The data for the fractures were summarized as odds ratios (OR), while total AE and SAE were summarized as risk ratio (RR) along with 95% confidence intervals (CI). The BMD was represented as pooled mean change. Review Manager Version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for estimation of a pooled effect by fixed effect model [23]. Heterogeneity was assessed using I^2 [24, 25]. I^2 greater than 50% was taken as significant heterogeneity. Sensitivity analysis was planned for high heterogeneity if inconsistency remains unexplained as per subjects, intervention, or outcomes. The interpretation of meta-analysis was done as per the results of the fixed-effect model [24, 26].

Assessment of quality of evidence—GRADE pro GDT analysis

For analyzing the overall quality of evidence, GRADE pro-GDT (guideline development tool) software was used [27]. The optimal information size (OIS) was calculated and it was found to be 1138 patients in each group. The final overall evidence quality as per the GRADE was classified as high, moderate, low, or very low. The GRADE pro GDT software was accessed online from the site: https://gradepro.org/ [27].

Results

Study selection

The PRISMA flow diagram represents the selection of studies and exclusion process (Supplementary Fig. 1). Out of a total of 179 records screened, data from 8 published RCTs and 2 unpublished RCTs [28, 29] were included for meta-analysis. Eight RCTs were published as 18 studies, out of which data of 12 studies were included [14–19, 30–35]. Six excluded published studies had duplicate results of eight RCTs that were included in the analysis.

Study characteristics

The characteristics of RCTs are summarized in Supplementary Table number 1. In the present analysis, a total of 10 RCTs were included with 6137 patients in romosozumab group and 5732 patients in the control group.

Risk of bias within the studies

The overall risk of bias (ROB) was assessed to be "Low" as all the included studies were assessed as having low ROB. There were no issues with the randomization, deviation from intervention, missing data, outcome measurement, or reporting of results. Hence, the ROB assessed for GRADE analysis was also considered to be low ROB. Unpublished RCT protocols were assessed from clinicaltrials.gov for assessment of ROB. The ROB of RCTs is represented in Fig. 1 and Supplementary Fig. 2 (Weighted summary ROB).

Efficacy outcomes

Fractures

Incidence of fracture data was taken from two RCTs with approximately 5367 and 5369 patients in ROMO and standard of care groups, respectively. A significant decrease in incidence of vertebral fractures at 12 months [OR = 0.51 (95%CI = 0.40–0.65), $p < 0.00001$; $I^2 = 86\%$] (Fig. 2a) and 24 months [OR = 0.43 (95%CI = 0.35–0.52), $p < 0.00001$; $I^2 = 87\%$] (Fig. 2b), nonvertebral fractures at 24 months [OR = 0.78 (95%CI = 0.66–0.92), $p = 0.003$; $I^2 = 0\%$] (Fig. 2c), and clinical fractures at 24 months [OR = 0.70 (95%CI = 0.60–0.82), $p < 0.00001$; $I^2 = 0\%$] (Fig. 2d) was observed with ROMO as compared to standard therapy. The high heterogeneity is due to difference in confidence interval of two studies and due to placebo use for first 12 months in FRAME study.

Risk of falls—Fig. 3

To analyze the risk of falls, data were included from four RCTs which approximately contained 6094 and 5935 patients in standard of care groups, respectively. The risk of falls was significantly decreased at 36 months [OR = 0.85 (95%CI = 0.77–0.95), $p = 0.003$; $I^2 = 0\%$] (Fig. 3). There was no difference in the risk of falls between the two groups when assessed in 12/24 months [OR = 1.59 (95%CI = 0.83

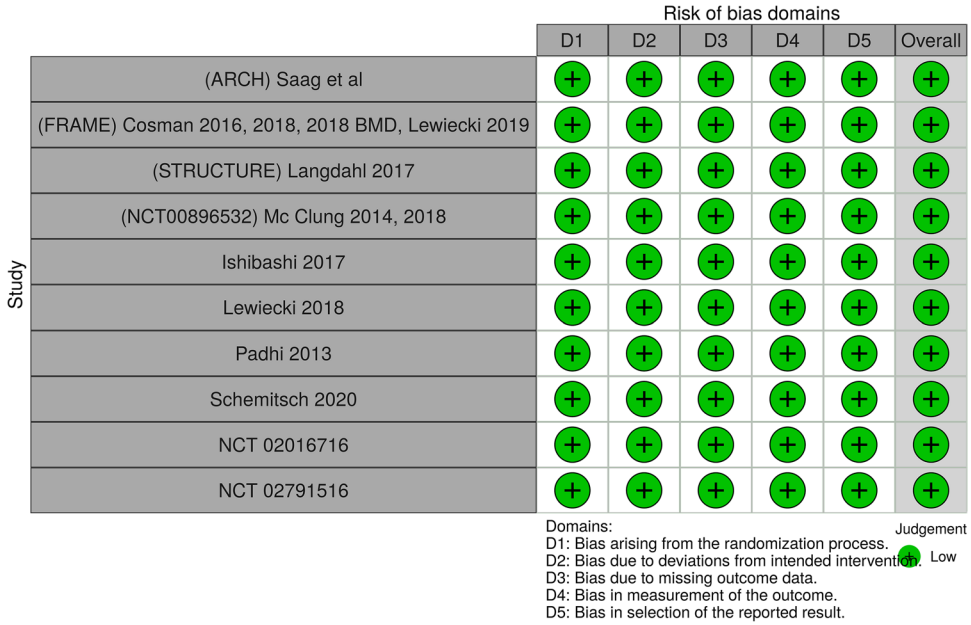

Fig. 1 ROB-2: risk of bias in RCT evaluating Romosozumab for treatment of post-menopausal osteoporosis

– 3.02), $p = 0.16$; $I^2 = 4\%$]. A significant reduction in risk of falls in the ROMO group was seen with pooled analysis of the data [OR = 0.87 (95%CI = 0.78–0.96), $p = 0.007$; $I^2 = 40\%$].

Percentage change in bone mineral density

To analyze the effect on BMD, the studies were divided into four groups. Firstly, studies analyzing BMD of the lumbar spine at 12 months were selected. Seven RCTs with a total of 3823 patients in the ROMO group and 3619 patients in the standard of care group respectively showed significant improvement in BMD with ROMO [mean difference (MD) = 12.66 (95%CI = 12.66–12.67), $p < 0.00001$; $I^2 = 100\%$] (Fig. 4a). Secondly, studies analyzing lumbar spine BMD at 24 months were clubbed. Two RCTs with 3251 patients in the ROMO group and 3195 patients in the standard of care group respectively also showed significant improvement in BMD with ROMO [MD = 11.10 (95%CI = 11.10–11.10), $p < 0.00001$; $I^2 = 93\%$] (Fig. 4b). Thirdly, studies with total hip BMD at 12 months were analyzed. Seven RCTs with 3771 and 3619 patients in the ROMO and standard of care group respectively showed a significant improvement in the hip BMD with ROMO [MD = 5.69 (95%CI = 5.68–5.69), $p < 0.00001$; $I^2 = 100\%$] (Fig. 5a). Finally, seven RCTs analyzing the BMD of the femoral neck at 12 months with 3771 and 3619 patients in ROMO and standard of care group respectively showed a significant improvement in the femoral neck BMD with ROMO [MD = 5.18 (95%CI = 5.18–5.19), $p < 0.00001$; $I^2 = 100\%$] (Fig. 5b).

Safety outcomes

Total adverse events

Eight RCTs were included for pooled analysis of the total adverse events(AE) with 6812 patients in the ROMO group and 6066 in the standard of care group respectively. No significant difference was observed with the total adverse events between the two groups [RR = 0.98 (95%CI = 0.96–1.01), $p = 0.15$; $I^2 = 45\%$] (Supplementary Fig. 3).

Serious adverse events

Pooled analysis of eight RCTs with included 6812 patients in the ROMO group and 6066 patients in the standard of care group revealed no significant risk of serious adverse events (SAE) in the ROMO group as compared to control [RR = 0.98 (95%CI = 0.88–1.08), $p = 0.64$; $I^2 = 23\%$] (Supplementary Fig. 4).

Publication bias

A total of ten RCTs were included for the analysis. A funnel plot of seven studies included in BMD analysis revealed graph is asymmetrical (Supplementary Fig. 5). Egger's regression test for funnel plot asymmetry revealed low publication bias for BMD ($t = 2.2788$, $p = 0.0716$). There was low publication bias for total adverse events ($t = 0.0030$, $p = 0.9977$) and risk of falls ($t = 2.0755$, $p = 0.1736$). Overall publication bias of the studies was taken as low.

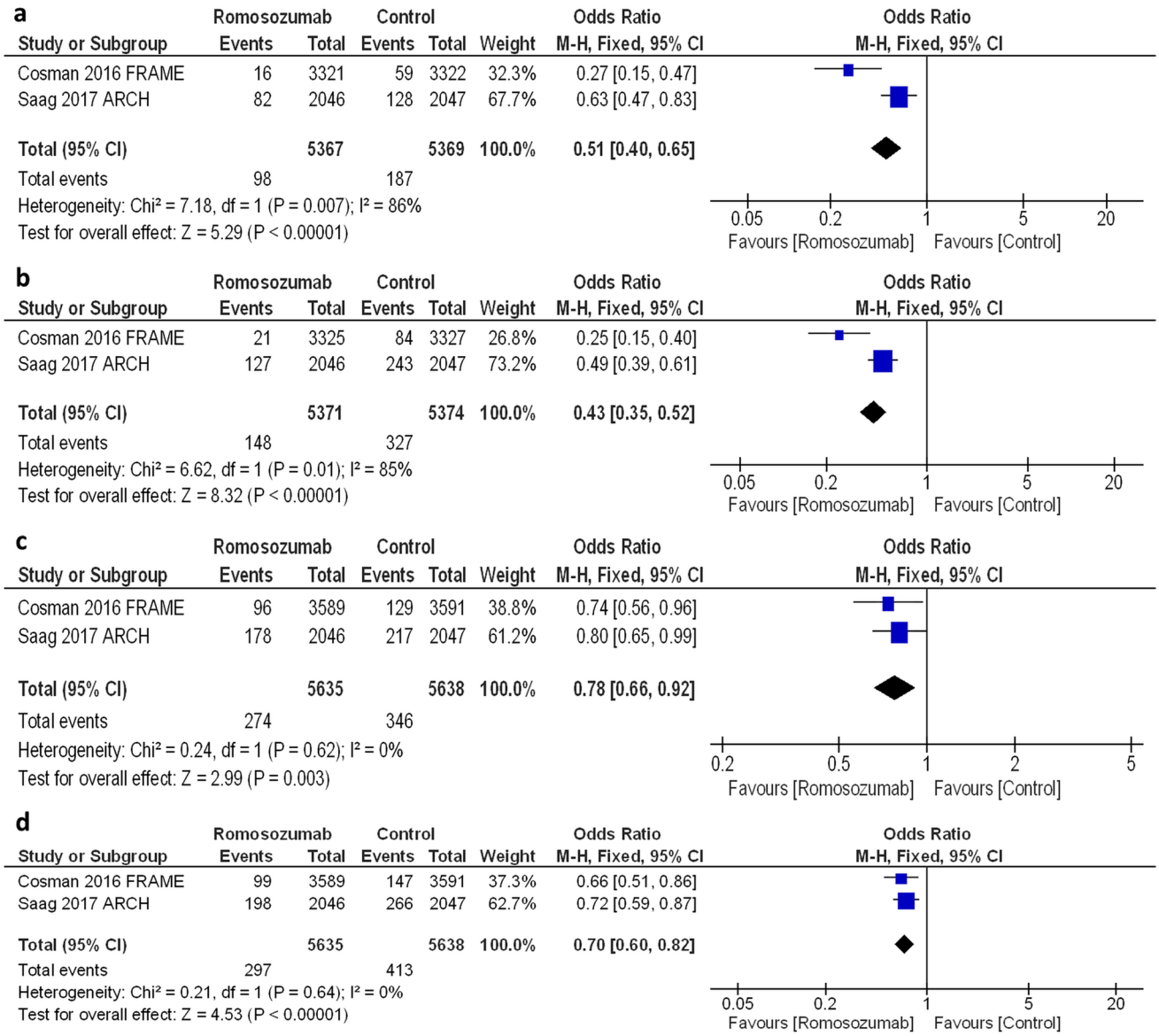

Fig. 2 Incidence of fractures in Romosozumab versus control group (2a vertebral fractures at 12 months, 2b vertebral fractures at 24 months, 2c nonvertebral fractures, 2d clinical fractures)

GRADE analysis of the primary and secondary outcomes (Table 1)

The GRADE Pro GDT analysis for fracture incidence was regarded as a "High" quality of evidence. This is due to low ROB of RCTs, low heterogeneity, and direct outcomes with regard to the patient in addition to high precision in results. The quality of evidence for BMD was graded as "Moderate". The GRADE recommendation for either outcome, i.e., total and serious AE was also recommended as "Moderate" quality evidence, as there was the presence of high imprecision. Overall, there was "HIGH" grading for systematic review as per GRADE pro GDT. The GRADE evidence quality for current systematic review is shown in Table 1.

Discussion

This article systematically reviewed 10 RCTs (8 RCTs were published as 12 articles and 2 unpublished RCTs) and it was observed that patients treated with ROMO showed a significant improvement in the BMD at the

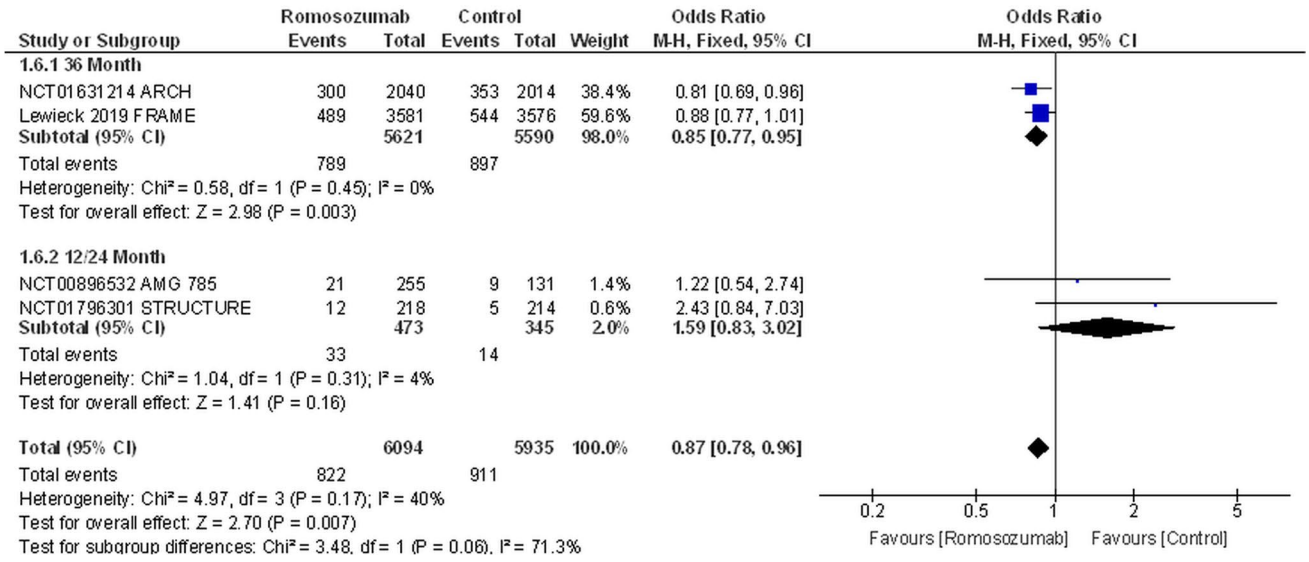

Fig. 3 Risk of falls in Romosozumab versus control group

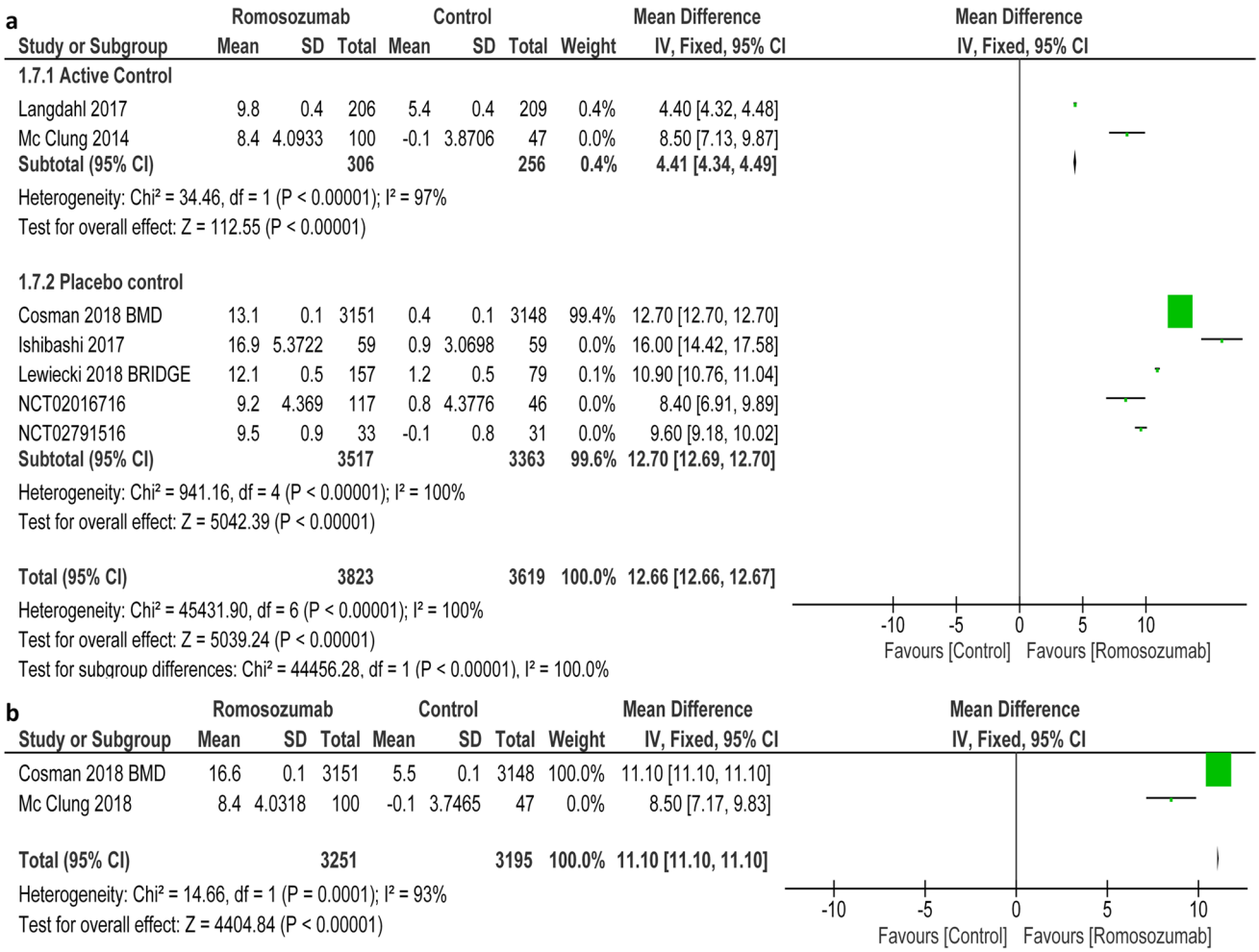

Fig. 4 Percentage BMD change at lumbar spine in Romosozumab versus control group (4a at 12 months, 4b at 24 months)

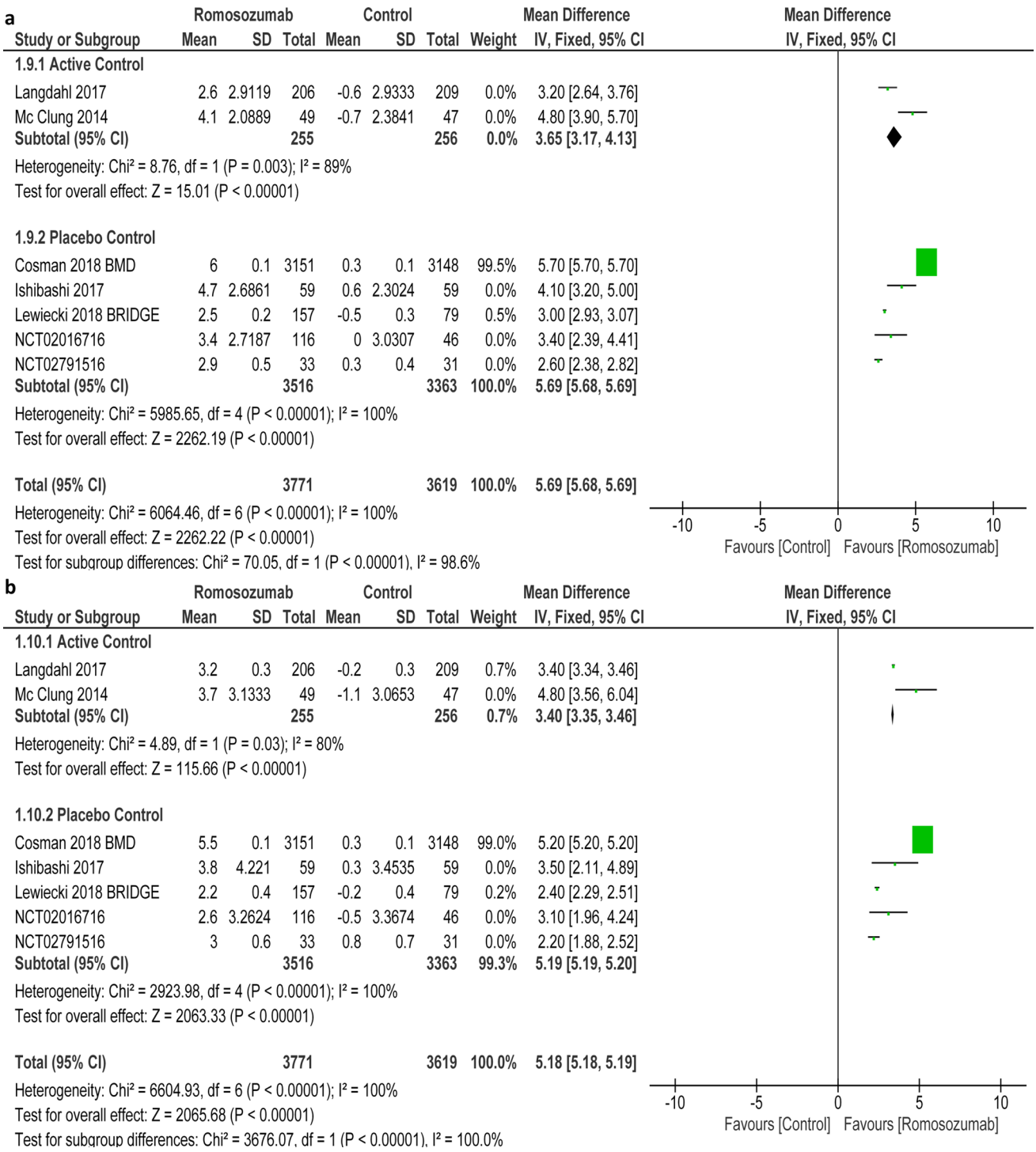

Fig. 5 Percentage BMD change in Romosozumab versus control group (5a total hip BMD at 12 months, 5b femoral neck BMD at 12 months)

lumbar spine, total hip, and femoral neck over a period of 12–36 months. ROMO was effective in significantly reducing the risk of fracture and risk of falls in postmenopausal women with osteoporosis. The adverse events with ROMO were comparable to the control groups.

The current study observed a significant decrease in vertebral fracture incidence at 12 months and 24 months, nonvertebral fractures, and clinical fractures with ROMO

Table 1 GRADE recommendation for primary and secondary outcomes for use of Romosozumab in post-menopausal osteoporosis

Certainty assessment						№ of patients		Effect		Certainty, importance
№ of studies Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Efficacy	Placebo	Relative (95% CI)	Absolute (95% CI)	
Vertebral fractures at 24 Months										
2 RCT	Not serious	Not serious [a]	Not serious	Not serious	Strong association	148/5371 (2.8%)	327/5374 (6.1%)	**OR 0.43** (0.35 to 0.52)	**34 fewer per 1,000** (from 39 fewer to 28 fewer)	⨁⨁⨁⨁ HIGH, CRITICAL
Nonvertebral fractures 24 or 36 Months										
2 RCT	Not serious	Not serious	Not serious	Not serious	None	274/5635 (4.9%)	346/5638 (6.1%)	**OR 0.78** (0.66 to 0.92)	**13 fewer per 1,000** (from 20 fewer to 5 fewer)	⨁⨁⨁⨁ HIGH, CRITICAL
Clinical fractures 24 or 36 Months										
2 RCT	Not serious	Not serious	Not serious	Not serious	None	297/5635 (5.3%)	413/5638 (7.3%	**OR 0.70** (0.60 to 0.82)	**21 fewer per 1,000** (from 28 fewer to 12 fewer)	⨁⨁⨁⨁ HIGH, CRITICAL
Risk of falls										
4 RCT	Not serious	Not serious	Not serious	Not serious	None	822/6094 (13.5%)	911/5935 (15.3%)	**OR 0.87** (0.78 to 0.96)	**17 fewer per 1,000** (from 30 fewer to 5 fewer)	⨁⨁⨁⨁ HIGH, IMPORTANT
BMD lumbar spine at 12 months										
7 RCT	Not serious	Not serious [b]	Not serious	Not serious	None	3823	3619	-	MD **12.66 higher** (12.66 higher to 12.67 higher)	⨁⨁⨁⨁ HIGH, IMPORTANT
BMD total hip at 12 months										
7 RCT	Not serious	Not serious [b]	Serious [c]	Not serious	None	3771	3619	-	MD **5.69 higher** (5.68 higher to 5.69 higher)	⨁⨁⨁◯ MODERATE, IMPORTANT
BMD femoral neck at 12 months										
7 RCT	Not serious	Not serious [b]	Serious [c]	Not serious	None	3771	3619	-	MD **5.18 higher** (5.18 higher to 5.19 higher)	⨁⨁⨁◯ MODERATE, IMPORTANT
Total adverse events										
8 RCT	Not serious	Not serious	Not serious	Serious [d]	None	4868/6812 (71.5%)	4320/6066 (71.2%)	**RR 0.98** (0.96 to 1.01)	**14 fewer per 1,000** (from 28 fewer to 7 more)	⨁⨁⨁◯ MODERATE, IMPORTANT
Serious adverse events										

Table 1 (continued)

Certainty assessment						№ of patients		Effect		Certainty, importance
№ of studies Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Efficacy	Placebo	Relative (95% CI)	Absolute (95% CI)	
8 RCT	Not serious	Not serious	Not serious	Serious [d]	None	738/6812 (10.8%)	660/6066 (10.9%)	**RR 0.98** (0.88 to 1.08)	**2 fewer per 1,000** (from 13 fewer to 9 more)	⨁⨁⨁◯ MODERATE, IMPORTANT

CI, confidence interval; *RR*, risk ratio; *OR*, odds ratio; *MD*, mean difference; *RCT*, randomized control trials

Explanations

a. Although I2 > 50%, heterogeneity is ignored as both the studies showed significant benefit as compared to control group

b. I2 > 50% is regarded as severe heterogeneity. As all studies showed an increase in BMD, heterogeneity is ignored. Hence, not downgraded for inconsistency

c. As bone mineral density is a surrogate marker for fractures. Hence, downgraded for indirectness

d. As 95% CI includes one, downgraded for imprecision

as compared to standard therapy. In support of our analysis, a meta-analysis conducted by Liu et al. also observed that ROMO was associated with significantly reduced risk of new vertebral fracture (RR = 0.37, 95% CI = 0.18–0.77, $p = 0.008$), nonvertebral fracture (RR = 0.79, 95% CI = 0.68–0.92, $p = 0.003$), and hip fracture (RR = 0.59, 95% CI = 0.42–0.83, $p = 0.002$) at 24 months [36].

A study conducted by Hernandez et al. reported that ROMO significantly minimized the risk of vertebral fractures while failed to reduce the risk of fractures at nonvertebral areas [37].

Cosman et al. reported that with romosozumab, the new vertebral fracture risk was 73% lower when comparing to the placebo group. Further, the clinical fracture risk was found to be 36% lesser in the ROMO group in contrast to placebo [14].

Saag et al. in their study reported that the risk of new vertebral fracture and clinical fractures at the 12th month with ROMO was lesser than with Alendronate (RR = 0.63; 95%CI 0.47–0.85) and (HR = 0.72; 95% CI, 0.54 to 0.96) respectively. The nonvertebral fracture risk was not decreased with ROMO [38].

The present review observed a significantly reduced risk of falls at 36 months but had no difference while assessing it on 12/24 months. Pooled analysis of the risk of falls showed a significantly reduced risk in the ROMO group as compared to the control group.

A meta-analysis by Mockel et al. reported a nonsignificant reduction in risk of falls by ROMO by 16% as compared to the control group (RR = 0.84; 95% CI, 0.67–1.04; $p = 0.10$) but a significant 12% reduction in risk of falls (RR = 0.88; 95%CI = 0.80–0.96; $p = 0.01$) when 12 months of ROMO was followed by 33–36 months of antiresorptive therapy [39].

Present analysis on the BMD of the lumbar spine at 12 and 24 months showed a significant gain in BMD with ROMO. Similar results were obtained with total hip and femoral neck BMD at 12 months with ROMO. Results of meta-analysis conducted by Liu et al. were in support of our analysis as they reported that ROMO significantly increased the BMD of the lumbar spine, total hip BMD, femoral neck BMD vs. placebo, vs. alendronate, and vs. teriparatide [36].

Kaveh et al. in their meta-analysis included only seven studies in their analysis. ROB was done using the Cochrane ROB-1 tool which is an old tool for analysis. In addition, the incidence of falls with the use of ROMO was also not reported. Kaveh et al. reported that ROMO 210 mg was significantly effective in improving lumbar spine BMD vs. Alendronate and placebo, but not vs. Teriparatide. Similar significant results were noted with ROMO 140 mg vs. placebo and ROMO 70 mg vs. placebo. The results for total hip BMD with ROMO 210 mg were significant versus alendronate as well as placebo. Similarly, there was significant

improvement in total hip BMD with ROMO 210 mg vs. Teriparatide, ROMO 140 mg vs. placebo, and ROMO 70 mg vs. placebo. Significant improvement in the femoral neck BMD was observed with ROMO 210 mg when compared with Alendronate, Teriparatide, and placebo. A similar significant improvement in BMD was seen with ROMO 140 mg as compared to placebo. However, no difference in BMD was observed with the use of ROMO 70 mg versus placebo [40].

A systematic review by Chen et al. reported that the gain in BMD with ROMO was higher than the placebo, teriparatide, and alendronate [41].

Our analysis observed that there was no significant difference in the total adverse events and serious AE between ROMO and the control group. In support of the present study findings, Liu et al. reported that they failed to find any significant difference in adverse events incidence in patients with ROMO vs. placebo, teriparatide, and alendronate respectively [36].

Marisca et al. reported no difference in total adverse events and serious adverse events with ROMO vs. placebo. However, there was a significant increase in AE with alendronate as compared to ROMO. The frequency of SAE with alendronate was higher than ROMO but was nonsignificant [42].

Kaveh et al. in their study reported no difference in the odds of any adverse events with ROMO as compared to alendronate but increased in comparison to teriparatide. There was no significant difference in AE, SAE, death, adjusted cardiovascular death, and cancer when ROMO 210 mg, 140 mg, and 70 mg as compared with placebo [40]. Although authors interpreted that there were decreased odds of deaths, CVS deaths, and increase odds of AE, SAE, and cancer with placebo as compared to ROMO. The interpretation by Kaveh et al. was not appropriate as none of the odds ratios achieved significance.

Romosozumab is a type of humanized monoclonal antibody that has an affinity for binding and blocking the activity of sclerostin, which is a cytokine present in our body and is responsible for blocking bone formation and enhancing bone resorption. Romosozumab shows a dual effect by enhancing bone formation and to an extent by decreasing the resorption of bones [43]. The Wnt signaling pathway is crucial for skeletal development, adult skeletal homeostasis, and bone remodeling [8]. Sclerostin is a well-known blocker of the Wnt signaling pathway. Based on the role of sclerostin as an osteocyte-derived inhibitor of osteoblastogenesis and bone formation, blocking sclerostin helps to increase bone formation by increasing bone matrix production by osteoblasts, and recruitment of osteoprogenitor cells hence increasing bone mass [13].

Limitations and strengths

The strength is that we did a GRADE analysis as per the GRADE Pro GDT recommendation. Overall GRADE recommends High-quality evidence.

Quality of evidence: (GRADE)

The overall quality of systematic review is "High." Critical outcomes like fracture incidence and change in BMD were regarded as high to moderate respectively. This evidence suggests that the inclusion of more high-quality RCTs is very unlikely to have any impact on our confidence in the estimate and unlikely to change the estimate.

Conclusion

High-quality evidence was generated from the current systematic review with regard to a significant decrease in fracture incidence with Romosozumab. Overall significant increase in BMD with moderate-quality evidence favors the use of Romosozumab in postmenopausal osteoporosis. No difference in total AE, as well as serious AE with Romosozumab with moderate-quality evidence, strengthens the recommendation of the use of the drug for the treatment of osteoporosis (High-quality evidence).

Further RCTs will be very unlikely to change the overall conclusion of the systematic review.

Abbreviations BPs: Bisphosphonates; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO: International Prospective Register of Systematic Reviews; ROMO: Romosozumab; ROB-2: The Risk of Bias -2 tool for randomized control trials; CI: Confidence interval; OR: Odd ratios; HR: Hazard ratios; GRADE pro GDT: Grades of Recommendations, Assessment, Development and Evaluations (GRADE) guideline development tool; OIS: Optimal information size; vs: Versus

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00198-021-06095-y.

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Author contribution Study design and planning of systematic review—All of the authors
Literature search—SD, SS
Figures—SS, SD, SK
Tables—JS, SK, SS
Data collection and analysis—SS, SBV
ROB—SD, SS, Query resolved by all authors
GRADE Analysis—SS Query resolved by all authors
Data interpretation—SS, SD, SK

Writing—SS, SD, TK
Corrections and Final approval of Manuscript—All of the authors
The corresponding author attests that all listed authors meet authorship criteria as per ICJME and that the manuscript is an honest, accurate, and transparent account of the study being reported.

Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on request.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Conflicts of interest None.

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