

Effects of romosozumab on bone mineral density and fractures in postmenopausal women: a meta-analysis

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Journal of the Ceylon College of Physicians, 2024, **55**, 29-35

Abstract

Purpose: Romosozumab, a mono-clonal antibody has been approved for the treatment of postmenopausal women with osteoporosis and high fracture risk. This meta-analysis evaluated the effect of romosozumab on Bone Mineral Density (BMD) and fracture occurrence in postmenopausal women with osteoporosis.

Methods: A systematic search was done adhered to the PRISMA guidelines in PubMed, Ovid and Clinicaltrials.gov and eligible studies were selected. The details related to study participants, changes in BMD at the lumbar spine (LS), total hip (TH) and femoral neck (FN) and the occurrence of fractures during the period were extracted. The mean differences of BMDs between the two groups and odds ratios (OR) of fractures were considered as the outcome of the studies.

Results: Of the 11 potentially eligible articles, only four studies fulfilled the selection criteria and they were included in the final analysis. Romosozumab therapy for 12 months increased mean BMD at the LS by 12.7% (95% CI, 9.7, 15.6), TH by 4.8% (95% CI, 3.3, 6.3) and FN by 4.1% (95% CI, 3.1, 5.2). Treatment with romosozumab decreased the odds of new vertebral fractures and vertebral fractures by 58% (OR=0.42, CI, 0.23, 0.91) and 25% (OR=0.75, CI, 0.53, 1.06) respectively at the end of 12 months.

Conclusion: Romosozumab significantly increases BMD at LS, TH and FN and reduces the risk of new

vertebral and non-vertebral fractures in postmenopausal women with osteoporosis.

Key words: bone mineral density, fractures, meta-analysis, osteoporosis, romosozumab

Introduction

Osteoporosis, the most prevalent metabolic bone disease particularly seen among postmenopausal women and older men,¹ has become a major health concern worldwide.² Although osteoporosis can lead to fracture at any skeletal site, spine, hip, ribs and forearm are the typical sites involved. Osteoporosis is not a health priority in many Asian countries which are still burdened with non-communicable diseases.³ Dong et al, studying the epidemiology of hip fracture from 1990 to 2019, reported global hip fracture incidence of 14.2 million per annum (95% CI, 11.1 to 18.1) and the associated years lived with disability of 2.9 million (95% CI, 2.0 to 4.0) in 2019. The authors conclude that hip fractures are common and devastating to those affected and economically burdensome to healthcare systems, globally.⁴ Furthermore, economic evaluations have reported high health and social care costs involved with hip fracture management in many countries including Japan,⁵ Ireland⁶ and France.⁷

Drugs used in osteoporosis can broadly be divided to two groups; anti-resorptives and anabolic drugs. Anti-resorptives prevent bone resorption and thereby preserve bone mineral density and are proven to reduce

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Received 07 December 2023, accepted 15 February 2024.



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either the first or subsequent fractures. Anabolics, in contrast to anti-resorptives, induce formation of bone material and also are proven to reduce fractures.⁸ Due to the limited efficacy and adverse effects inherited to the existing therapies, newer medications are being introduced to expand the treatment options in osteoporosis. Apart from new therapies, newer treatment modalities have been introduced in the recent years. This includes sequential therapy where patients switch to different drug after completing the full period of treatment with the first medication.⁹

Romsozumab is a novel humanized monoclonal antibody which inhibits a protein involved in the regulation of bone formation called sclerostin and thereby it promotes bone formation and inhibits bone resorption.¹⁰ Clinical studies with romsozumab have shown significant improvements in bone mineral density (BMD) at hip and spine.^{11,12} Further, the incidence of new vertebral fractures dramatically reduced following treatment with romsozumab for 12 months compared to either placebo or bisphosphonate in patients with postmenopausal osteoporosis.¹³ At the beginning of this study the efficacy of romsozumab, however, was mostly limited to individual studies with a solitary meta-analysis.

The primary objective of the current study was to estimate the overall effect of romsozumab on BMD and fracture occurrence in postmenopausal women with osteoporosis using meta-analysis approach. In this analysis, the primary endpoints were percentage changes BMD at the lumbar spine (LS), total hip (TH) and femoral neck (FN) and the occurrence of fractures during the study period.

Material and methods

This study was done adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and data extraction was done using keywords “romsozumab” and “randomized clinical trials” first in the PubMed and subsequently in other databases such as Ovid, Embase and Clinicaltrials.gov. The PubMed search was done both as free-text and MESH searches to enhance the sensitivity. Two authors (S. L & G. L) selected eligible studies, independently and blinded to each other, using the following selection criteria and disagreements were resolved after consensus. Inclusion criteria; randomized controlled clinical trials, using romsozumab as the

treatment, on postmenopausal women, follow-up period 12 months, reporting on BMD, fracture, or both. Exclusion criteria: studies reporting bone markers or histology, animal studies, non-English language publications and cohort and case-control studies. Data extracted included first author, year of publication, number of subjects in two groups and outcomes. The mean percentage changes in BMD from the baseline at LS, FN and TH, and all types of incident fractures were considered as the outcome measurements.

Quality assessment of selected studies

The Jadad score was used to assess the quality of the trials included in this analysis. The overall score ranges from 0 to 5, with higher values signifying better reporting. The quality assessment was carried out by two authors (S. L & G. L) and discrepancies and conflicts were settled by agreement and arbitration by authors.¹⁴

Statistical analysis

Meta analysis refers to the quantitative method of synthesis pooled effect size from many studies that examine a certain topic.¹⁵ In this study, we analyzed the mean percentage changes of BMD and the incidence of fractures, separately. Mean differences and the odds ratios (OR) were calculated for continuous (percentage changes in BMD) and dichotomous (fractures reported or not) outcomes, respectively. Data were analyzed using R 4.2.2 statistical software.

Fixed and random effect models for meta-analysis

In meta-analysis, there are two accepted models, the fixed effect model and the random effect model.¹⁶ In this study, we used Cochran Q test and I^2 index to determine the heterogeneity.¹⁷

Results

Study selection and characteristics

Among the 11 eligible articles, four studies were included in this meta-analysis (Figure 1) and Table 1 contains a detailed description of them. Fractures were categorized into three types: new vertebral fractures (NV), vertebral fractures (V) and clinical fractures (C). According to the Jadad score, all selected studies got more than 3 score.

Meta-analysis

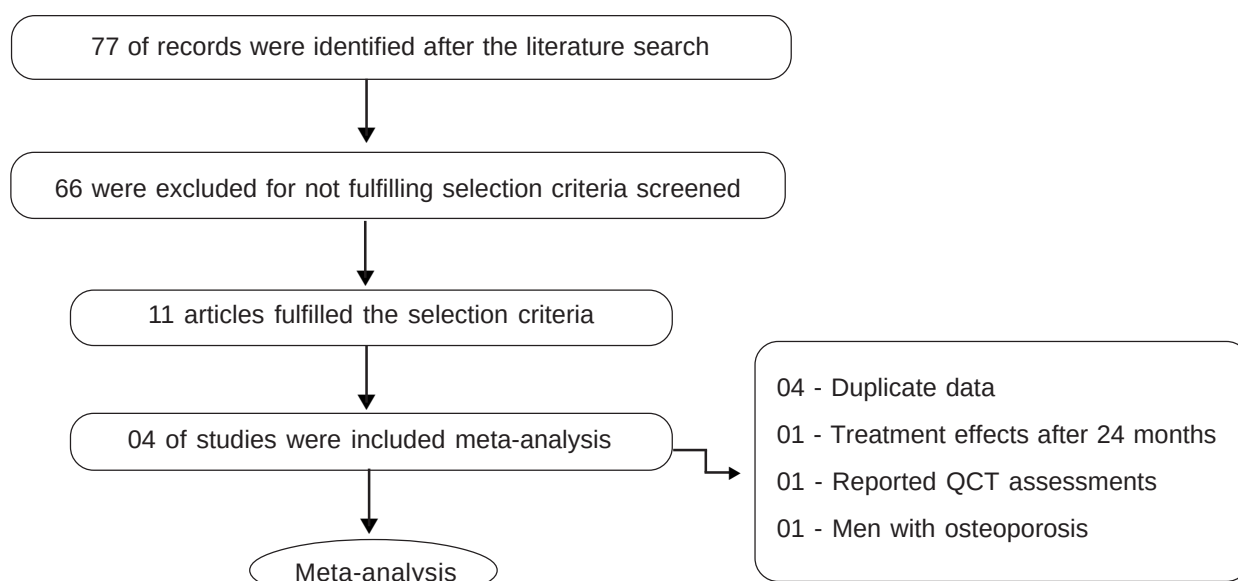


Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram.

Table 1. Description of the four clinical trials included in the analysis

First Author, (Year)	Duration (months)	Sample size		Mean percentage change BMD (SD)		No. of fractures	
		Treatment	Control	Treatment	Control	Treatment	Control
Kenneth G. Saag, (2017) ¹⁸	12	2046	2046	13.7 (0.3) [LS] 6.2 (0.2) [TH] 6.2 (0.2) [FN]	5.0 (0.3) [LS] 2.8 (0.2) [TH] 2.8 (0.2) [FN]	82 [NV]	128 [NV]
Hideaki Ishibashi (2017) ¹¹	12	63	63	16.9 (1.4) [LS] 5.7 (0.7) [TH] 3.8 (1.1) [FN]	0.9 (0.9) [LS] 1.3 (0.7) [TH] 0.4 (0.9) [FN]	1 [V]	1 [V]
F. Cosman (2016) ¹⁹	12	3321 65* [LS] 66* [TH] 66* [FN]	3322 61* [LS] 62* [TH] 62* [FN]	13.3 (1.3) [LS] 6.8 (0.9) [TH] 5.2 (2.0) [FN]	0.0 (0.5) [LS] 0.0 (0.7) [TH] -0.7 (2.2) [FN]	16 [NV] 56 [V]	59 [NV] 75 [V]
Harry K Genant (2016) ²⁰	12	24* [LS] 9* [TH] 9* [FN]	27* [LS] 18* [TH] 18* [FN]	12.3 (1.5) [LS] 3.9 (1.8) [FN] 3.9 (1.8) [TH]	-0.4 (1.5) [LS] -0.7 (1.4) [TH] -0.7 (1.4) [FN]	NR	NR

Abbreviations: LS, lumbar spine; FN, femoral neck; TH, total hip; NR, not reported; NV, new vertebral; V, vertebral; C, clinical.

* Sample sizes for BMD analysis

Meta-analysis showed high heterogeneity in BMD in the LS, TH and FN, therefore random effect meta-analysis models were applied. The results in meta-analysis illustrate the mean (95% CI) percentage BMD changes in the LS, TH and FN, respectively. In meta-

analysis, the pooled effect sizes (% BMD increase and Confidence Intervals (CI)) found were; 12.7 (9.7,15.6) in LS, 4.8 (3.3,6.3) in TH and 4.1 (3.1,5.2) in FN at 12 months (Table 2).

Mean percentage changes in BMD

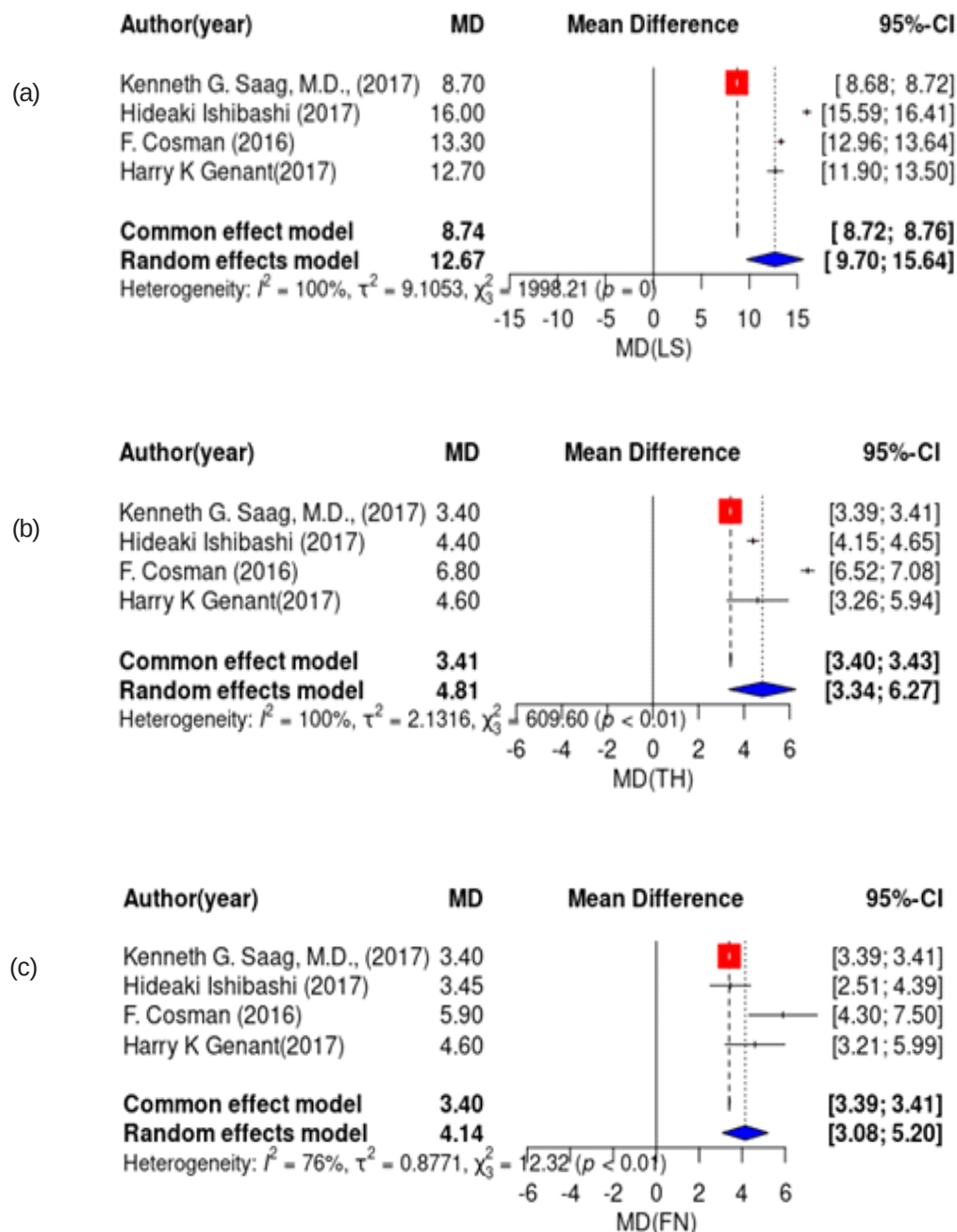


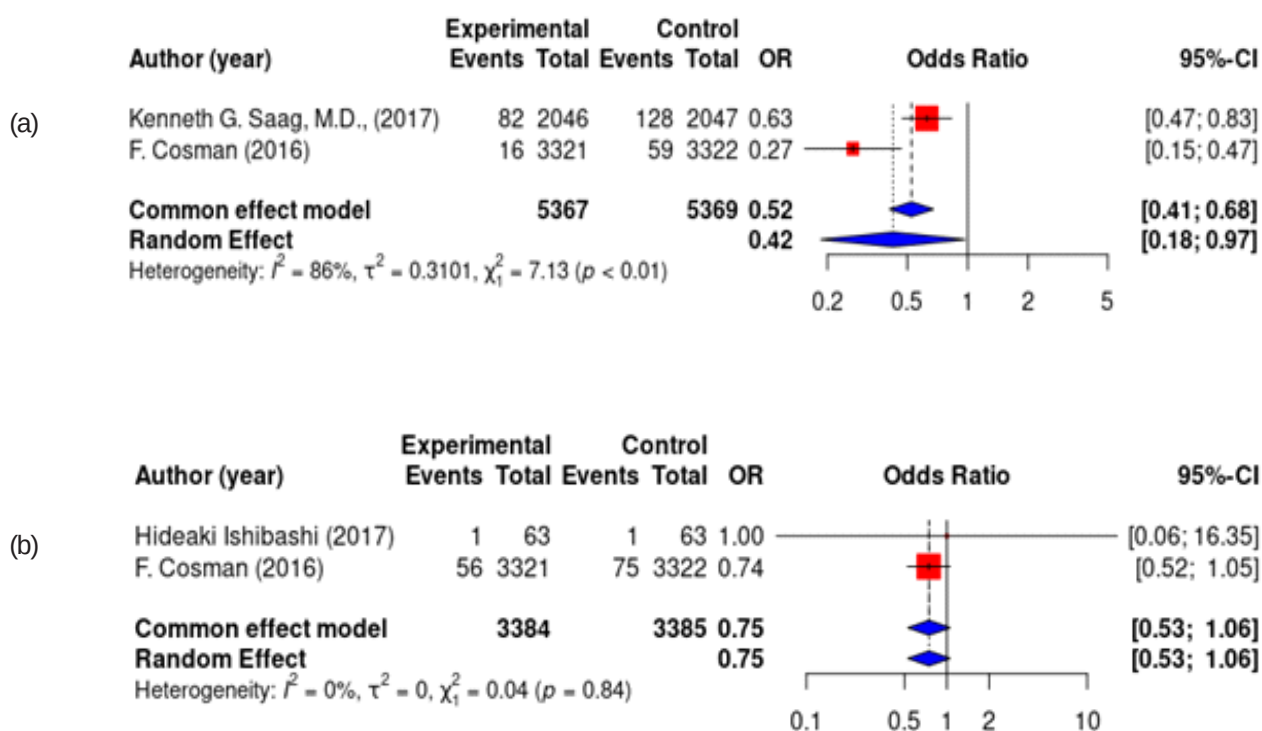
Figure 2. Forest plots for Bone Mineral Density changes in the (a) Lumbar Spine (b) Total Hip and (c) Femoral Neck.

Table 2. Meta-analysis of the effect of romosozumab on mean percentage change in BMD

<i>Duration of Treatment</i>	<i>LS</i>	<i>TH</i>	<i>FN</i>
12 months	12.67 (9.70,15.64)	4.81 (3.34,6.27)	4.14 (3.08,5.20)

Abbreviations: LS, lumbar spine; FN, femoral neck; TH, total hip

Anti-fracture efficacy of romosozumab



**Figure 3. Forest plot of the (a) incidence of new vertebral fractures
(b) incidence of vertebral fractures after 12 months.**

Meta-analysis showed high heterogeneity in the new vertebral fractures, therefore random effect meta-analysis model was applied. Furthermore, it showed low heterogeneity in the vertebral fractures, therefore fixed effect meta-analysis model was applied.

Treatment with romosozumab showed a significant reduction of odds of new vertebral fractures by 58% (OR=0.42, 95% CI, 0.18, 0.97) and no reduction of the odds of vertebral fractures by 25% (OR=0.75, 95% CI, 0.53, 1.06) at the end of 12 months.

Table 3. Odd ratios and 95% CIs associated with romosozumab on different fracture types

<i>Duration of Treatment</i>	<i>New Vertebral</i>	<i>Vertebral</i>	<i>Clinical vertebral</i>
12 months	0.42 (0.18,0.97)	0.75 (0.53,1.06)	*

Publication bias

The funnel plot (Figure 4) shows no publication bias in our meta-analysis. This is further confirmed by the Egger's test with p-value of 0.64.

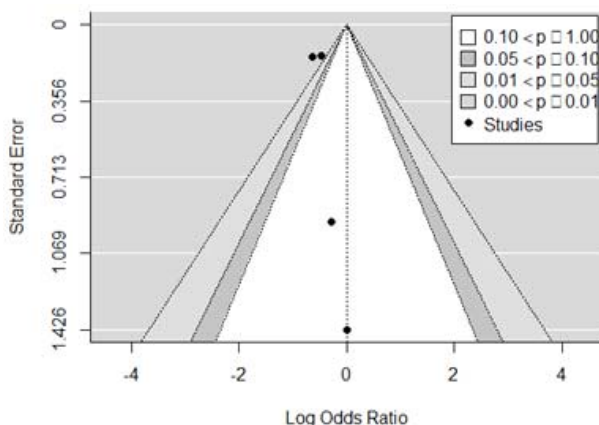


Figure 4. Funnel plot for log odds ratio after 12 months

Discussion

This study illustrates the summary statistics of the meta-analysis of romosozumab on BMD and fracture occurrence incorporating data from randomized controlled clinical trials. In this analysis, it was found that 12 months treatment with romosozumab increases BMD at LS, FN and TH and reduces new fractures. The BMD gains with 12 months treatment were 12.7% at LS 4.8% at TH and 4.1% at FN. Furthermore, romosozumab treatment decreased the odds of all fractures by 42% (OR 0.58; 95% CI, 0.47, 0.70).

The occurrence of new vertebral fractures and vertebral fractures were significantly lower in the romosozumab group compared to placebo group at the end of 12 months. Twelve months of romosozumab treatment reduced the odds of new vertebral fractures by 58% and this was statistically significant. The 25% reduction of vertebral fracture risk after 12 months treatment, however, was non-significant as the upper limit of the 95% CI was marginally higher than 1, most likely due the fewer number of study subjects. This appears more an inconclusive outcome than a negative outcome.²¹

A recent meta-analysis by Huang et al.²² examined the efficacy of romosozumab in the treatment of new vertebral fractures (RR=0.52, CI, 0.41,0.67). However, in our results, the efficacy of romosozumab treatment

of new vertebral fractures is higher than the previous study (OR=0.42, 95% CI, 0.18,0.97). Compared with the previous study, the current study indicated more efficacy with the romosozumab treatment for new vertebral fractures. The efficacy of romosozumab for vertebral fractures was similar to the findings of the previous meta-analysis. The reason for obtaining a higher efficacy for new vertebral fractures might be the duration of the studies we recruited. In our meta-analysis we recruited only the studies which were 12 months, whereas the previous meta-analysis recruited studies which were conducted for 3 months and 6 months as well.

The findings from this study should be considered with the several limitations we encountered. These include limited number of studies, short follow up period and missing data. Further, some trials did not report fracture data while some did not include standard deviations of the BMD and also log (OR). In addition, the corresponding standard deviations of the mean changes in BMD were estimated from the graphs published in the original manuscripts. The corresponding standard deviations for the log (OR) were estimated using the formulae which used in the random effect UVMA in the frequentist approach. Fractures were reported as new vertebral, vertebral and clinical with the limited information on specific types of fractures; therefore, we analyzed only the effect of romosozumab on new vertebral and vertebral fractures after 12 months. Due to the small number of combined trials, the bivariate meta-analysis was not applied; therefore, the correlation between the two outcomes; BMD and fractures was not considered.

Author declaration

Competing interests

There are no conflicts of interests.

Ethics approval

This study used published data, therefore ethical approval was not required.

Authors contribution

DM: Analysis, interpretation of results in the study, wrote the original draft text and prepared all the figures of the manuscript. JL: Design of the study, provided the methodology, interpretation of the results, reviewed and edited the manuscript. LG: Extracted and checked the validation of the data, interpretation of data for the study, reviewed and edited the manuscript. LS: Design of the study, extracted and checked the validation of the data, reviewed and edited the manuscript, provided the final approval of the version to be published.

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