

Denosumab in the treatment on structural damage caused by rheumatoid arthritis: a systematic review and meta-analysis

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Research article

Keywords: denosumab, rheumatoid arthritis, structural damage, safety

Posted Date: April 12th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-393365/v1>

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic inflammatory joint disease, which can cause cartilage and bone damage as well as disability. The effects of denosumab in patients with RA have been analyzed in several clinical studies. These results provide strong evidence to suggest that denosumab significantly inhibited the progression of bone erosion, increased BMD in patients with RA. We undertook a meta-analysis to summarize the efficacy and safety of denosumab in the treatment on structural damage caused by rheumatoid arthritis.

Methods: We searched PubMed, Embase, Medline, The Cochrane Library, and collected randomized controlled trials of denosumab in patients with rheumatoid arthritis from the database was established until January 19, 2021. Literature was screened according to inclusion and exclusion criteria, and RevMan 5.3 software was used for Meta-analysis after quality assessment.

Results: Five eligible studies were included in the primary meta-analysis. Denosumab significantly inhibited the increase of the modified Sharp erosion score (MD=-0.62, 95%CI -0.91 to -0.33, P=0.0001) and modified total Sharp score (MD=-0.78, 95%CI -1.23 to -0.33, P=0.0007) compared to placebo groups at 12 months. In addition, denosumab also significantly increased lumbar spine BMD (3.73, 95% CI 2.00, 5.46, P<0.0001) compared to placebo or bisphosphonates. There was no evidence of an effect of denosumab on joint space narrowing. Adverse events, serious adverse events were similar between denosumab and placebo arms.

Conclusion: Results suggest that denosumab inhibits the progression of structural damage caused by rheumatoid arthritis, with no increase in the rates of adverse events as compared with control group. Preliminary research suggests that denosumab is reasonable and promising options for preventing and treating structural destruction in rheumatoid arthritis.

Trial registration: We registered our study with PROSPERO (registration number CRD42021239783); no other meta-analysis focusing on denosumab use for structural damage caused by rheumatoid arthritis were found in the PROSPERO database.

Background

Rheumatoid arthritis is the most common inflammatory arthritis and is a major cause of disability. (1) In industrialized country, rheumatoid arthritis affects 0.5–1.0% of adults, with 5–50 per 100 000 new cases annually. It seriously affects people's health. (2) Clinical studies have demonstrated Methotrexate as well as targeted synthetic DMARDs (e.g., Janus kinase inhibitors) effectively suppresses disease activity in patients with RA, not only reduce joint inflammation but also ameliorate joint destruction in RA. (3–7) However, the joint-protective effect of these reagents is not complete and they are frequently accompanied by serious adverse effects such as infection as a result of immune system suppression. (8) Recent studies have demonstrated that osteoclasts are responsible for bone destruction in RA. (9) Bone loss is a hallmark of RA, bone erosions and 'periarticular' bone loss directly affect the joint architecture

and lead to impairment of joint function. Erosions in RA are the consequence of the induction of bone resorbing osteoclasts, while at the same time osteoblasts are suppressed.(10, 11)Since osteoclast differentiation and activity are key events in arthritic bone damage, the signals that trigger osteoclastogenesis are potential therapeutic targets. (12)

Denosumab is a fully human monoclonal IgG2 antibody that binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. Denosumab prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors, prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone,(13–15) as a treatment for osteoporosis in men and post-menopausal women at high risk of fractures,(16, 17)as well as for the treatment of bone loss associated with androgen-deprivation therapy for prostate cancer in men at high risk of fractures(18), glucocorticoid-induced osteoporosis (GIOP)(19)and bone destruction due to rheumatoid arthritis (RA) or metastatic cancers.(20) Clinical research reports in recent years, denosumab significantly inhibited the progression of bone erosion and no difference in the risk of side effects compared to placebo.(21–23) Other studies shows that compared with treatment by biological disease-modifying antirheumatic drugs (bDMARDs) alone, concurrent use of denosumab and bDMARDs in RA patients was efficacious in inhibiting structural damage.(24) Combining denosumab with disease modifying anti-rheumatic drugs may be considered for RA patients with progressive bone erosions. (25)The purpose of this systematic review and meta-analysis is to summarize published data describing the efficacy and safety of denosumab in the treatment on structural damage caused by rheumatoid arthritis.

Materials And Methods

We searched PubMed, Embase, Medline, The Cochrane Library from the database was established until January 19, 2021 using the terms “denosumab,” “rheumatoid arthritis,” “bone erosion,” “structural damage” and “safety.” Studies in any language were included. Two authors independently reviewed the abstracts of all publications to determine eligibility. We searched PubMed to determine whether relevant abstracts presented at these meetings were subsequently published. If not published, we next contacted authors via email to inquire on the date of anticipated publication. We updated our literature search in January 2021.

Studies were included if they recruited subjects clinically diagnosed patients with rheumatoid arthritis with varying degrees of bone destruction, used denosumab and control arm, and assessed the effect of treatment on modified Sharp erosion score and safety. We excluded review articles, case reports and case series. Figure 1 summarizes the total number of articles identified and reasons for exclusion.

Both authors independently extracted data from included publications including the year of publication, number of subjects assigned to control and denosumab therapy, and study outcomes including changes

in modified Sharp erosion score, modified total Sharp score, modified Sharp joint space narrowing score, bone mineral density(BMD) and side effects.

Both authors independently rated the quality of each included publication, using the Cochrane quality assessment for intervention studies. One author prepared a table summarizing details of the included studies. (Table 2)

Statistical analysis

We performed using RevMan 5.3 software, and the inspection level was $\alpha = 0.05$. The χ^2 test analysis was used to test the homogeneity of the relevant literature included in the study. If $I^2 < 50\%$, the fixed effects model should be used for analysis, and if $I^2 \geq 50\%$, the random effects model should be used for analysis. After treatment, continuous variables such as Sharp scores were studied using standardized mean difference (MD), and non-continuous variables such as adverse reactions were used relative risk ratio (RR). The interval estimates were all based on 95% confidence intervals (95% CI). (26)The funnel chart was used to assess publication bias. If the funnel chart shows that most of the studies are in the upper part of the "inverted funnel chart" and the bottom part is less, and the left and right sides are basically symmetrical, it indicates that the publication bias is not obvious; otherwise, it indicates that there is a significant publication bias. Our primary analyses focused on the five trials comparing denosumab to control group.

Results

From our literature search, we identified 226 articles of interest. After screening for eligibility based on the aforementioned inclusion criteria, 214 articles were excluded (Fig. 1). We assessed the remaining 14 full-length articles for eligibility. Of these, 9 publications were excluded due to lack of a control or no focus on bone erosion caused by rheumatoid arthritis, leaving 5 publications for inclusion in the meta-analysis. (Table 1) and the paragraphs below summarize the main findings of these studies.

Cohen et al(21) reported a twelve-Month, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase II Clinical Trial comparing the effects of denosumab and placebo on Structural Damage, Bone Mineral Density, and Bone Turnover in rheumatoid arthritis patients.(21)The trial was sponsored by Amgen Incorporated (Thousand Oaks, CA, USA). The analysis focused on changes in modified Sharp score among 138 participants,rheumatoid arthritis patients received subcutaneous placebo, denosumab 60 mg, or denosumab 180 mg injections every 6 months for 12 months. Herein, we report the results for the placebo and 60 mg denosumab arms, since the 60 mg dose is FDA approved for osteoporosis in postmenopausal women and men. A significant difference in the modified Sharp erosion score was observed as early as 12 months in the 60mg denosumab group ($P = 0.012$) as compared with placebo. There was no evidence of an effect of denosumab on joint space narrowing. Rates of adverse events were comparable between the denosumab and placebo groups.

Takeuchi, T. et al(22) reported effect of denosumab on Japanese patients with rheumatoid arthritis: a dose–response study of AMG 162 (Denosumab) in patients with rheumatoid arthritis on methotrexate to Validate inhibitory effect on bone Erosion (DRIVE)– a 12-month, multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial. The analysis focused on changes in modified Sharp erosion score among 160 participants, patients with RA between 6 months and < 5 years, stratified by glucocorticoid use and rheumatoid factor status, were randomly assigned to subcutaneous injections of placebo or denosumab 60 mg every 6 months (Q6M), every 3 months (Q3M) or every 2 months (Q2M). The primary endpoint was change in the modified Sharp erosion score from baseline to 12 months. Denosumab significantly inhibited the progression of bone erosion at 12 months compared with the placebo, and the mean changes of the modified Sharp erosion score at 12 months from baseline were 0.99, 0.27 (compared with placebo, $p = 0.0082$) and also significantly inhibited the increase of the modified total Sharp score compared with the placebo, with no obvious evidence of an effect on joint space narrowing for denosumab. No apparent difference was observed in the safety profiles of denosumab and placebo.

Takeuchi, T. et al(23) reported effects of the anti-RANKL antibody denosumab on joint structural damage in patients with rheumatoid arthritis treated with conventional synthetic disease modifying antirheumatic drugs (DESIRABLE study): a randomized, double-blind, placebo-controlled phase 3 trial. The analysis focused on changes modified total Sharp score. Denosumab groups showed significantly less progression of joint destruction. The mean changes in the modified total Sharp score at 12 months were 1.49 (95% CI 0.99 to 1.99) in the placebo group, 0.99 (95% CI 0.49 to 1.49) in the Q6M group ($p = 0.0235$). The mean changes in bone erosion score were 0.98 (95% CI 0.65 to 1.31) in the placebo group, 0.51 (95% CI 0.22 to 0.80) in the Q6M group ($p = 0.0104$). No significant between-group difference was observed in the joint space narrowing score. No major differences were observed among safety profiles.

Hasegawa, T. et al(24) reported efficacy of denosumab combined with bDMARDs on radiographic progression in rheumatoid arthritis. Compared with treatment by bDMARDs alone, concurrent use of denosumab and bDMARDs in RA patients was efficacious in inhibiting structural damage.

In our meta-analysis, we focused on four studies(21–24) comparing changes in modified Sharp erosion score between participants randomized to experimental or control. In these studies, participants receiving denosumab or denosumab plus bDMARDs had a greater inhibited the increase of the modified Sharp erosion score compared to those receiving placebo or bDMARDs alone ($-0.58, 95\% \text{ CI } -0.84, -0.32$ $P < 0.0001$, Fig. 2) with low study heterogeneity ($I^2=0\%$). Likewise, participants assigned to experimental group had a greater inhibited the increase of the modified total Sharp score compared to control ($-0.63, 95\% \text{ CI } -1.06, -0.21$ $P = 0.004$, Fig. 3) with low study heterogeneity ($I^2=0\%$). There was no evidence of an effect of experimental group on joint space narrowing score ($P = 0.37$, Fig. 4). We found adverse events, serious adverse events were similar between denosumab and placebo arms ($1.05\%, 95\% \text{ CI } 0.77, 1.43, P = 0.75$, Fig. 6) with low heterogeneity among the 3 studies ($I^2=0\%$).

In our meta-analysis, we focused on four studies(21–23, 25)comparing changes in bone mineral density(BMD) between participants randomized to experimental or control. In these studies, denosumab prevented a decrease in lumbar spine BMD and significantly increased the BMD compared to control (3.73, 95% CI 2.00,5.46 P < 0.0001, Fig. 5) .

Cochrane quality assessment indicated that five studies were of good quality, and they were of excellent quality(Table 2).

Discussion

Rheumatoid arthritis is a prevalent autoimmune disease characterized by the inflammation of multiple synovial joints followed by joint destruction and deformity,the expression of RANKL in rheumatoid arthritis patients and found that synovial fibroblasts express RANKL and induce osteoclastogenesis.(27) Anti-RANKL antibodies, the most direct method to suppress bone destruction.Denosumab is currently the most active RANKL inhibitor that can be used in human treatment. It binds with RANKL with high affinity to inhibit the interaction of RANKL and RANK, inhibits the formation and function of osteoclasts, thereby reducing bone resorption, increasing bone mass, and improving bone strength,(28) were approved for rheumatoid arthritis in Japan in 2017, and be added to the indication for the inhibition of rheumatoid arthritis with bone erosion in 2020. Initiating the targeting of osteoclasts in the treatment of rheumatoid arthritis is one of the important fruits of osteoimmunology.(29) We performed a meta-analysis of five randomized-controlled trials evaluating the efficacy and safety of denosumab in the treatment of rheumatoid arthritis. These results provide strong evidence to suggest that denosumab can prevent the progression of bone erosion in RA patients.(30)Treatment with denosumab significantly greater increments in lumbar spine BMD compared to placebo or bisphosphonate therapy. No apparent difference was observed in the safety profiles of denosumab and placebo. Notably, however, denosumab treatment has little or no effect on cartilage deterioration or disease activity.

In addition, patients with RA are at increased risk of osteoporotic fractures. Denosumab has additional benefits for patients with RA by preventing osteoporosis.(31–34)Some studies show denosumab treatment increased BMD and reduced bone turnover markers regardless of baseline BMD or marker levels or concomitant bisphosphonate or glucocorticoid use.(35–37)

We acknowledge several limitations of our study. First, there were few randomized-controlled trials that met our criteria for inclusion in the meta-analysis, leading us to include a retrospective cohort study designs. Second, all studies were short in duration (12 months), thus the long-term efficacy and safety of denosumab for rheumatoid arthritis cannot be addressed at this time. Third, the medication and treatment courses of the included studies are not exactly the same. Due to the small number of included studies, it is impossible to conduct subgroup analysis based on the treatment courses. Therefore, whether the clinical efficacy between different courses of treatment is the same, still needs further verification. Finally,among the 5 studies included, only 3 reported adverse reactions. Other literature reported that no adverse reactions were found during the observation period. It is not ruled out that there are some milder

adverse reactions that may be eliminated by human factors, or some late-onset adverse reactions. Not counted due to short observation time.

In conclusion, data from this systematic review and meta-analysis indicate that denosumab is a reasonable drug to prescribe, in the treatment of rheumatoid arthritis. Denosumab inhibits the progression of structural damage caused by rheumatoid arthritis and effectively increase BMD with no increase in the rates of adverse events. Based on our literature review and meta-analysis, preliminary research suggests that denosumab is reasonable and promising options for preventing and treating structural destruction in rheumatoid arthritis.

Conclusions

The collective data from five clinical trials shows that denosumab therapy significantly inhibited the increase of structural damage caused by rheumatoid arthritis. The collective data from the completed trials showed no difference in the risk of mild or serious side effects between people who took denosumab compared to placebo.

Abbreviations

RA, rheumatoid arthritis; BMD, bone mineral density; FDA, Food and Drug Administration; RANKL, receptor-activator nuclear kappa B ligand; bDMARDs, biological disease-modifying antirheumatic drugs; JSN, joint space narrowing; mTSS, modified total Sharp score; GIOP, Glucocorticoid-induced osteoporosis.

Abbreviations

RA, rheumatoid arthritis; BMD, bone mineral density; FDA, Food and Drug Administration; RANKL, receptor-activator nuclear kappa B ligand; bDMARDs, biological disease-modifying antirheumatic drugs; JSN, joint space narrowing; mTSS, modified total Sharp score; GIOP, Glucocorticoid-induced osteoporosis.

Declarations

Acknowledgements

We would like to thank the researchers and study participants for their contributions.

Authors' contributions

Sx.W. and S.C. designed the research. S.C. and Ah.Z. collected the data. S.C. wrote the paper. Bk.C. and Q.B. help optimize the research and proofread the paper. The authors read and approved the final manuscript.

Funding

This work was supported by the Military Medical Youth Growth Project of PLA General Hospital (QNC19005).

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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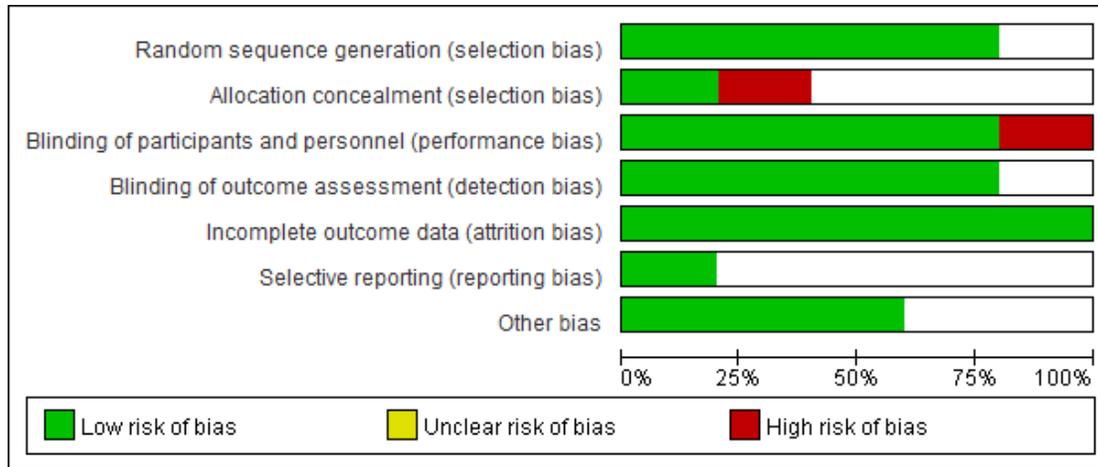
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Tables

Table 1 Characteristics of included literature

Study, year	Study design	Sample size	Study intervention and duration	Primary endpoint	Study outcome
Cohen, S. B.2008	multicenter, randomized, double-blind, placebo-controlled, phase II study in patients with rheumatoid arthritis	146 entered, 138 completed	Placebo or denosumab 60 mg or denosumab 120 mg at 0 and 6 months x12 months	Change in structural damage in patients with rheumatoid arthritis	Denosumab inhibited structural damage, Rates of adverse events were comparable between the denosumab and placebo groups.
Takeuchi, T.2015	multicenter, randomized, placebo-controlled phase II study in patients with rheumatoid arthritis	174 entered, 160 completed	Placebo or denosumab 60 mg every 6 months (Q6M), every 3 months (Q3M) or every 2 months (Q2M).	change from the baseline in the modified Sharp erosion score	Denosumab significantly inhibited the progression of bone erosion, No apparent difference was observed in the safety profiles of denosumab and placebo
Takeuchi, T.2019	multicenter, randomized, double-blind, parallel-group, placebo-controlled phase 3 study in patients with rheumatoid arthritis	454 entered, 407 completed	Placebo or denosumab 60 mg every 6 months (Q6M), every 3 months (Q3M).	change from the baseline in the modified total sharp score	Denosumab significantly less progression of joint destruction, no major differences were observed among safety profiles
Hasegawa,T.2016	Single centre, retrospective cohort study in patients with rheumatoid arthritis	80 entered, 80 completed	Experimental group:RA patients treated with denosumab plus bDMARDs for 12 months control group: treated with bDMARDs alone for 12 months	change from the baseline in the modified Sharp erosion score mTSS JSN score	Compared with treatment by bDMARDs alone, concurrent use of denosumab and bDMARDs in RA patients was efficacious in inhibiting structural damage without increasing adverse events
Yue, J.2016	randomized-controlled trial	40 entered, 40 completed	Patients receive either subcutaneous denosumab (60mg) once or oral alendronate (70mg) weekly for 6 months.	Change in the dimension (width, depth and volume) as well as the degree of marginal osteosclerosis of bone erosions; Change in BMD	the bone mineral density (BMD) of the erosion margin significantly increased only after treatment by denosumab comparable alendronate

Table 2 Quality evaluation of included literature



Figures

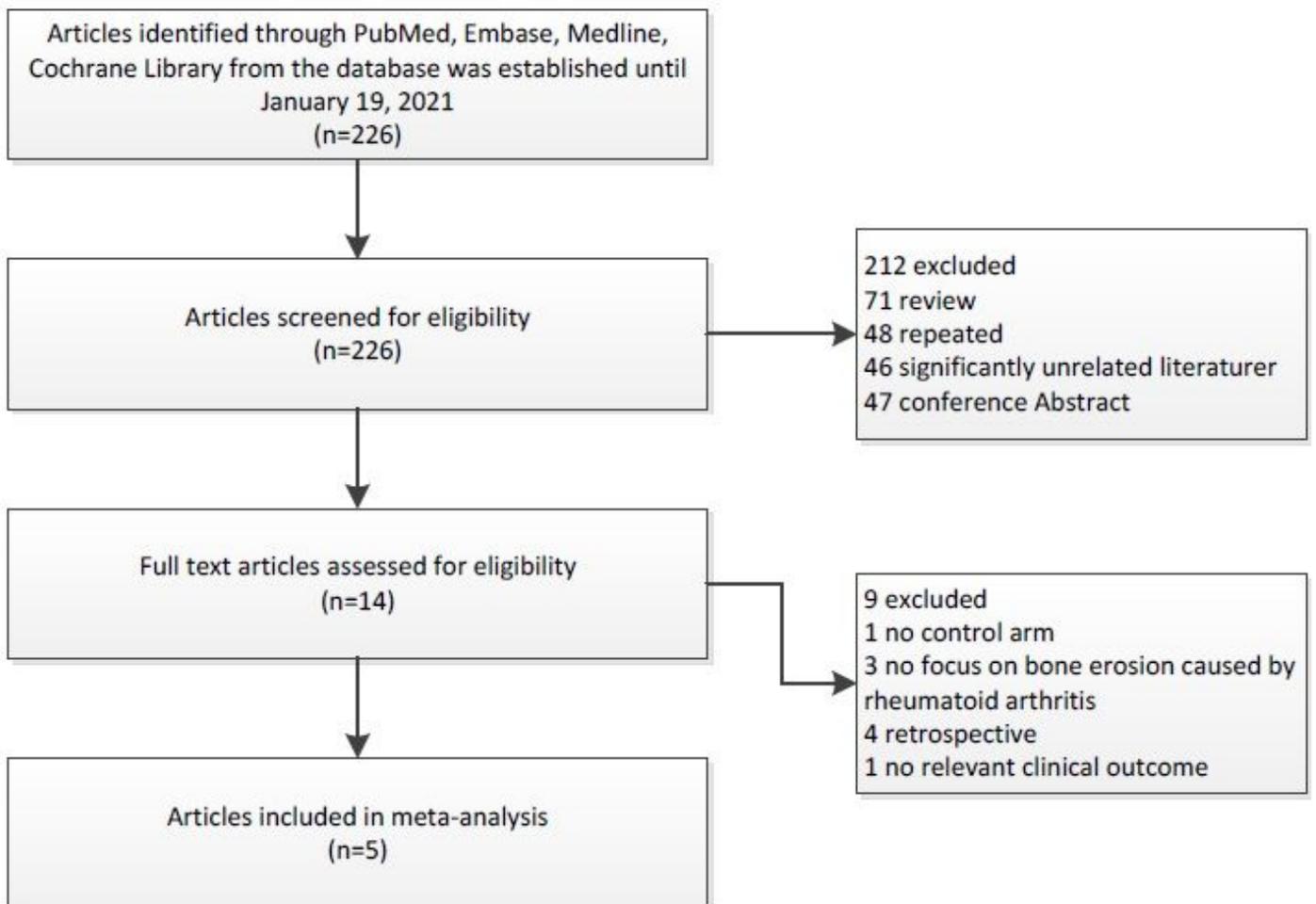


Figure 1

Flow diagram of literature search and study inclusion

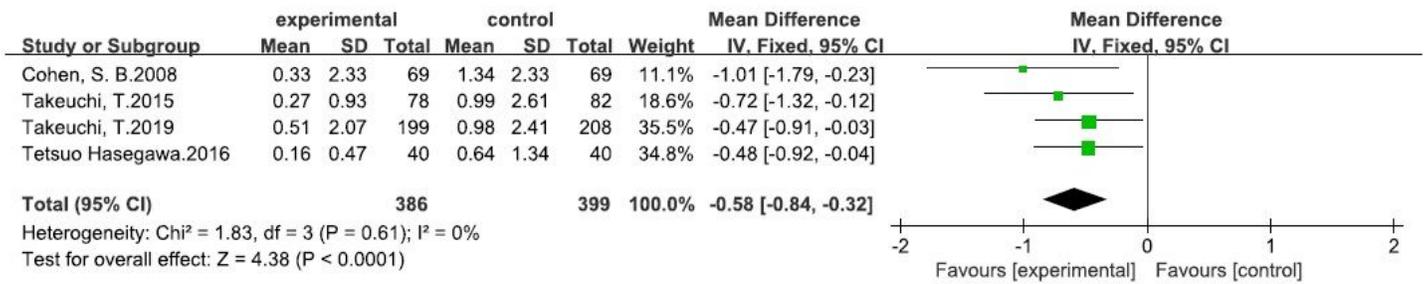


Figure 2

Percent change in modified Sharp erosion score between between two groups

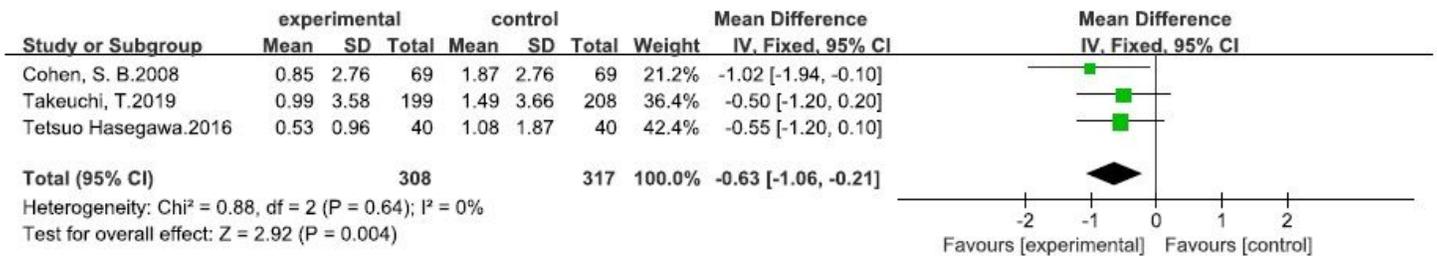


Figure 3

Percent change in mTSS between between two groups

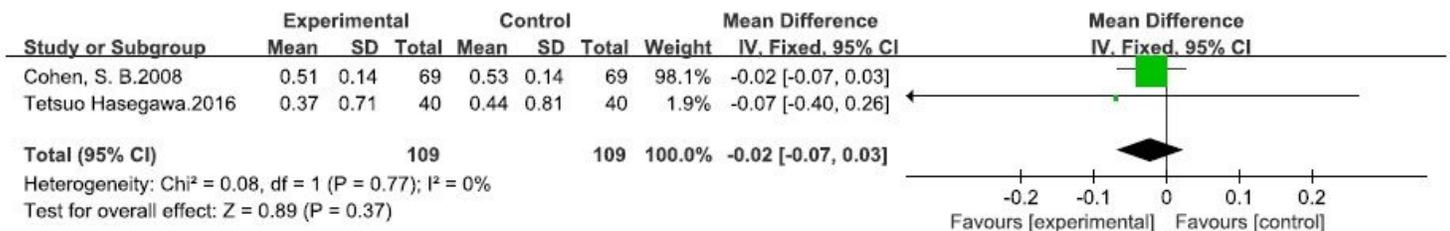


Figure 4

Percent change in JSN score between two groups

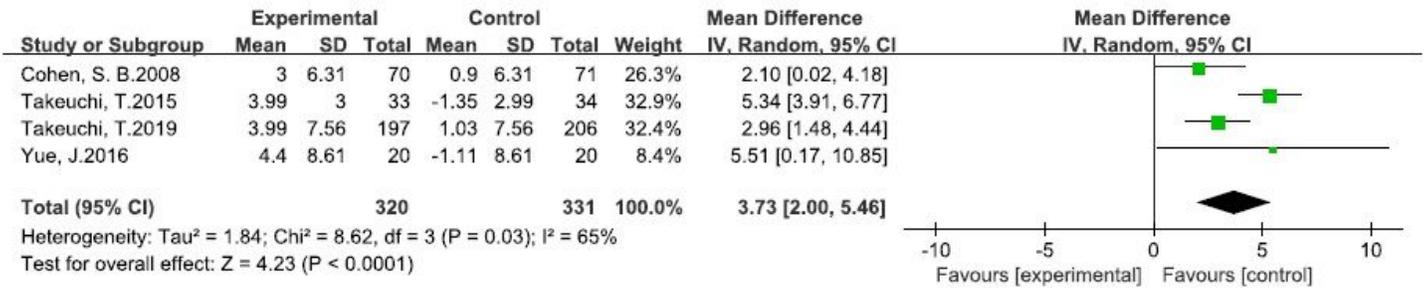


Figure 5

Percent change in BMD between two groups

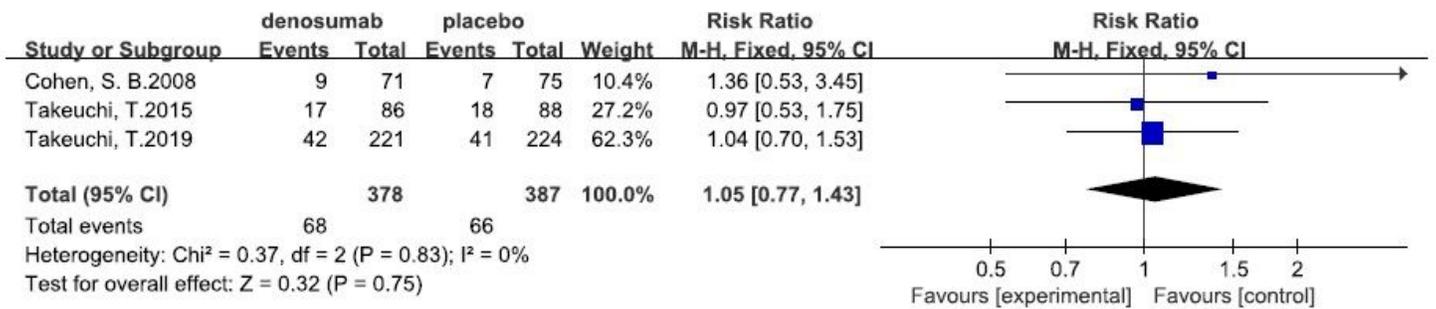


Figure 6

Percent change in incidence of adverse event between two groups