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META-ANALYSIS

Denosumab regimens in the treatment of giant cell tumor of bone: A systematic review with meta-analysis

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Abstract

BACKGROUND

Giant cell tumor of bone (GCTB) is a rare, locally aggressive neoplasm that should be treated surgically, whenever possible. This treatment approach may be linked with greater morbidity besides functional impairment. Denosumab is a human monoclonal antibody. Its administration inhibits bone resorption and has become part of the therapeutic armamentarium against GCTB, as it allows local control with a view to downstaging for a more conservative surgical procedure. However, there is no consensus in the literature regarding the optimal denosumab regimen for GCTB. Therefore, a wide discussion of denosumab regimen is necessary.

AIM

To assess the effectiveness of various therapy protocols employing denosumab in individuals with GCTB.

METHODS
A broad and systematic literature search was carried out using the PRISMA guidelines. We analyzed studies that reported skeletally mature patients with GCTB regardless of sex or ethnicity treated with denosumab. Articles with fewer than five patients and in languages except Spanish, Portuguese and English were excluded. Statistical analysis with proportion meta-analysis was performed due to the dichotomous nature of the data.

RESULTS
1005 articles were screened, of which 26 articles met the inclusion criteria and were selected, totaling 1742 patients, 51.8% women and 48.2% men, with an average of 35 years of age. Treatment with denosumab was associated with high rates of clinical benefit (CB) and imaging response (IR), without changing local recurrence rates when compared to patients treated without denosumab, regardless of the therapeutic regimen adopted and the number of doses applied. The adverse events (AE) presented were mostly mild, with the exception of a malignant transformation to osteosarcoma.

CONCLUSION
Treatment of GCTB with denosumab is effective, showing high rates of CB and IR. The AE that occurred were mostly mild. We found no differences between the articles considering the researched outcomes regardless of the therapeutic regimen adopted.

Key Words: Bone neoplasms; Denosumab; Outcome assessment health care; Giant cell tumor of bone; Systematic review

Core Tip: This systematic review with meta-analysis of proportions sought to evaluate the effectiveness of various denosumab-containing therapeutic regimens in the treatment of giant cell tumor of bone in terms of clinical outcomes, imaging response (IR), local recurrence (LR), and adverse events. Denosumab proved to be effective in inducing clinical response and IR, without impact on LR, regardless of the regimen and number of doses.

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DOI: https://dx.doi.org/10.5312/wjo.v16.i3.102520

INTRODUCTION

Giant cell tumor of bone (GCTB) is a rare, locally aggressive, benign primary neoplasm which accounts for approximately 5% of all bone tumors[1,2].

Histologically, GCTB is composed of reactive multinucleated osteoclast-like giant cells that express the receptor activator of nuclear factor kappa-B (RANK) and by mononuclear tumor stromal cells that express RANK ligand (RANKL) [1,3]. GCTB predominantly occurs in the third to fifth decades of life, however it can arise at any point of time in life, with a little female predilection. The most common locations of involvement are epiphysial–metaphyseal segments of the long bones surrounding knee (proximal tibia and distal femur), following to the distal radius[1,4,5]. It is rarely found in the axial skeleton[6]. Metastatic dissemination is rare, occurring in approximately 1% of cases[1,5,7,8]. GCTB does also have the potential for malignant transformation[1,4,6].

The clinical symptoms of GCTB involve limited range of motion, joint effusion, edema, and pain[1]. Plain radiography of the affected segment is the cornerstone of imaging and is the method of choice for initial evaluation of primary bone tumors, according to the American College of Radiology Appropriateness Criteria[9,10]. On radiographic inspection, GCTB initially appears as an eccentric, epiphyseal-metaphyseal lesion, lytic, involving precisely demarcated rim and no reactive sclerosis; however, when diagnosis is overlooked, progression may transpire swiftly, accompanied by cortical breakthrough and involvement of soft tissues resulting in extra-compartmental spread[5]. Supplementary imaging modalities (bone scintigraphy, computed tomography, magnetic resonance imaging) are needed to estimate local extension and examine for distant spread[9,10].

GCTB is treated surgically whenever possible[11]. Local disease control is essential to reduce the possibility of metastatic spread and/or LR. Few researchers have confirmed that wide resection reduces recurrence rates[12]. Nevertheless, this approach might be linked with greater functional impairment and morbidity[11,12]. As most affected patients are young adults and the majority of lesions are juxta-articular, the preferred treatment approach should include absolute elimination of the tumor while preserving the function of the affected limb[11,12]. The most common therapeutic intervention approaches involve intralesional curettage (to preserve the joint), alone or combined with adjuvant local treatment (electrocautery; instillation of absolute ethanol, phenol, or H_2O_2, among other substances) and filling with bone graft, bone substitutes, or polymethyl methacrylate[1,3,5,13-15].

Denosumab is a human monoclonal antibody exhibiting high affinity for RANKL. Its administration prevents RANKL/RANK binding and activation of the multinucleated osteoclast-like giant cells, thereby inhibits bone resorption. This medication has been utilized in the therapeutic intervention of bone metastases, osteoporosis and, recently, it had become component of medicinal armamentarium against GCTB, especially for unresectable lesions or when surgical treatment would involve *en bloc* resection or amputation, as it permits local control with a view to downstaging for a more conservative surgical procedure[1,4,16-18].

The objective of our study is to assess the effectiveness of dissimilar denosumab-containing treatment regimens in individuals with GCTB in terms of clinical outcomes clinical benefit (CB), imaging response (IR), local recurrence (LR), and adverse events (AE), in addition to age- and sex-related secondary outcomes.

MATERIALS AND METHODS

Study registration

This systematic review was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols guidelines[19,20] and was registered in the International Prospective Register of Systematic Reviews with accession number CRD42020190503. The protocol for this systematic review has been previously described and published[21].

Inclusion criteria

Type of study: Controlled or uncontrolled, randomized or non-randomized clinical studies and case series of at least five patients with GCTB treated with denosumab were included. Studies published in languages other than, Portuguese, Spanish, or English were excluded.

Patient profile: Skeletally mature patients with GCTB confirmed by histopathological examination were included, with no restrictions on gender or ethnicity.

Outcome measures: Denosumab regimen adopted, including dose, loading dose, and duration of treatment in number of doses (> 6 doses, ≤ 6 doses, and not reported); Response to denosumab, based on the treatment regimen, in terms of clinical outcomes (CB), IR, LR, and AE, in addition to secondary outcomes related to age (in years) and sex[21].

Search strategy

A methodical search was conducted in the ScienceDirect/Elsevier, SciELO, EMBASE (via Periódicos CAPES), MEDLINE (PubMed) and Cochrane Library databases, as well as in clinical trial registries (ClinicalTrials.gov and Registro Brasileiro de Ensaios Clínicos), with no restrictions on date of publication. To explore the gray literature, the Open Access Theses and Dissertations and Brazilian Digital Library of Theses and Dissertations databases were searched. We also performed a snowball search to find more references by searching the reference lists of publications eligible for full-text review to retrieve previously unidentified studies. Full search strategy has also been published in Barreto *et al*[21].

The Medical Subject Headings, EMBASE Subject Headings, and Health Sciences Descriptors controlled vocabularies were used for the search queries. Terms were crossed and/or grouped with Boolean operators "OR" and "AND", as presented in Table 1.

Screening and data extraction

Database searches were performed and the results imported into EndNote® reference management software, which removed duplicates. The results were exported to the Rayyan systematic review web-based application[22] and two other authors (Barreto BG and Moreira FD) independently screened the articles by abstracts as well as titles, thus finding studies potentially eligible for full-text reading. All study selection methods were based on PRISMA flow diagram (Figure 1). Any disagreements were resolved by the third author (Guedes A).

Data were extracted and arranged in a Microsoft Excel® spreadsheet ("Microsoft Corporation, 2019"). This information included the age, number, sex, and location of tumor in study participants; year, author and country of publication; treatment regimens adopted (doses, gaps amid doses, duration of treatment, *etc.*); and results (treatment response, LR, AE *etc.*). To avert bias in the data extraction method, two researchers (Barreto BG and Moreira FD) conducted it independently.

Risk of bias assessment (methodological quality)

The risk of bias in the selected studies was assessed independently by two raters (Guedes A and Paz CLD). The evaluation of the quality of the studies was carried out using the tool developed by the National Institutes of Health with a checklist for each type of study, ranging from nine to 12 questions. Each study was evaluated by answering "yes", "no", "cannot determine", "not applicable", or "not reported" for each of the checklist items (Supplementary Table 1).

Statistical analysis

Data analysis and processing: Per protocol[21,23], all statistical analyses were carried out in the R version 3.5.2 software environment (The R Foundation for Statistical Computing), running the "meta" package (version 4.9-6). Due to the dichotomous nature of the results, event and total data were extracted for clustering in a meta-analysis of proportions. As suggested by Schwarzer *et al*[24], data were pooled by a generalized linear mixed model containing random effects, using

Table 1 Database search strategy

Databases	Strategy
MEDLINE *via* PubMed	1 "Giant Cell Tumor of Bone"[Mesh] OR osteoclastoma; 2 "Denosumab"[Mesh] OR (Xgeva) OR (AMG 162) OR (Prolia); 3 1 AND 2
SciELO	1 "Giant Cell Tumor of Bone" OR "Tumor Óseo de Células Gigantes" OR "Tumor de Células Gigantes do Osso" OR Osteoblastoma; 2 Denosumab OR Xgeva OR AMG 162 OR Prolia OR Denosumabe; 3 1 AND 2
EMBASE	1 'osteoclastoma'/exp OR (giant AND cell AND tumor AND of AND bone) OR (giant AND cell AND tumor, AND bone) OR (giant AND cell AND tumour AND of AND bone) OR (giant AND cell AND tumour, AND bone) OR (polyostotic AND osteoclastoma); 2 'denosumab'/exp OR (amg AND 162) OR amg162 OR amgiva OR prolia OR xgeva; 3 1 AND 2
ScienceDirect	1 ("Giant Cell Tumor of Bone" OR osteoclastoma) AND (Denosumab OR Xgeva OR AMG 162 OR Prolia)
Cochrane Library	1 MeSH descriptor: [Giant Cell Tumor of Bone] explode all trees; 2 osteoclastoma; 3 1 OR 2; 4 MeSH descriptor: [Denosumab] explode all trees; 5 Xgeva; 6 AMG 162; 7 Prolia; 8-4 OR 5 OR 6 OR 7; 6-3 AND 8
Clinicaltrials.gov	1 (Giant Cell Tumor of Bone OR osteoclastoma) AND (Denosumab OR Xgeva OR AMG 162 OR Prolia)
Registro Brasileiro de Ensaios Clínicos	1 (Giant Cell Tumor of Bone OR osteoclastoma) AND (Denosumab OR Xgeva OR AMG 162 OR Prolia)
Open Access Theses and Dissertations	1 ("Giant Cell Tumor of Bone" OR osteoclastoma) AND (Denosumab OR Xgeva OR AMG 162 OR Prolia)
Biblioteca Digital Brasileira de Teses e Dissertações	1 ("Giant Cell Tumor of Bone" OR osteoclastoma) AND (Denosumab OR Xgeva OR AMG 162 OR Prolia)

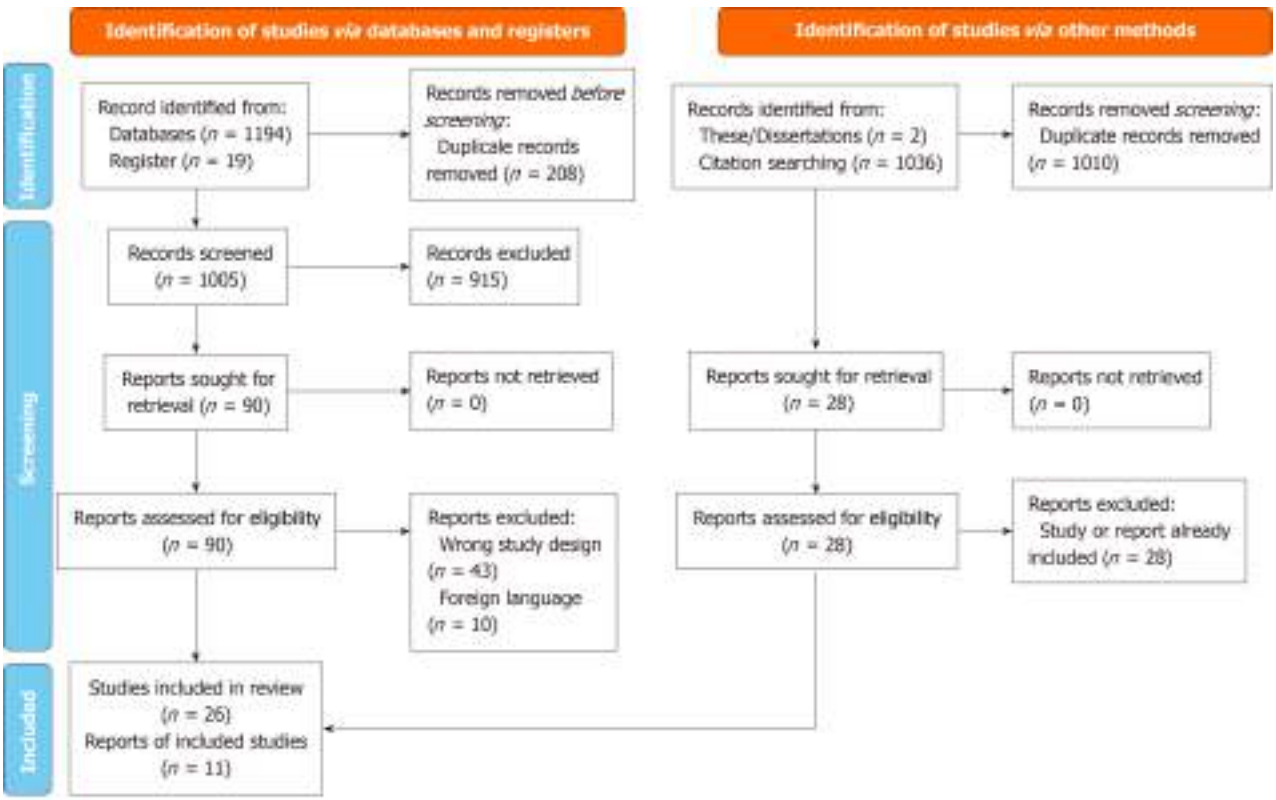


Figure 1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers, and other sources.

logit transformation of proportions, while the confidence intervals of individual studies were calculated using the Clopper-Pearson method.

To assess publication bias, a contour-enhanced funnel plot was constructed and visually inspected for asymmetry only if there were 10 or more studies in the analysis, as recommended by Sterne *et al*[25]. Sensitivity analyses by methodological design of the studies were used to evaluate their influence across the different types of studies on the pooled findings. The characteristics of each treatment regimen were investigated by a sensitivity analysis for denosumab dosage.

For each outcome, study heterogeneity was assessed with Cochran's χ^2 test, assuming evidence of heterogeneity at a P value < 0.10. The inconsistency of results across studies was assessed using the I^2 statistic. Descriptive thresholds for I^2 interpretation were adopted as follows: > 75%, high heterogeneity; ≥ 50%, substantial heterogeneity; < 50%, low hetero-

geneity.

RESULTS

Overall, 26 studies were selected (Figure 1), enrolling a total of 1742 patients, 896 (51.8%) female and 834 (48.2%) male–only one study[26] did not report the gender of the participants (n = 12). The mean age was 35 years, ranging from 13 to 81 years; five articles did not report minimum and maximum age[27-31], only the mean age, which in these publications ranged from 29 to 34 years (Table 2 and Table 3).

The denosumab regimen adopted for the treatment of GCTB in most studies consisted of 120 mg administered subcutaneously every 4 weeks with loading doses of 120 mg on days 8 and 15; only Sahito *et al*[32] used a weekly subcutaneous dose of 120 mg for 4 weeks. What did vary substantially between studies was the duration of denosumab therapy and the number of doses administered. Among the 26 studies, ten[17,27,30,31,33-38] used more than six doses, ten used six or fewer doses[27,29,32,39-45], and six[26,46-50] did not report the total number of doses received by participants (Supplementary Table 2).

CB

Seven studies[17,27,36-38,43,46] comprising 754 patients, evaluated the effect of denosumab on CB. The pooled findings demonstrated a CB rate of 89% (95%CI: 77%-95%), however, significant heterogeneity (τ^2 = 1.1096; P < 0.01) and high inconsistency (I^2 = 71%) of results were observed (Figure 2A).

Sensitivity analysis

When evaluating clinical trials only[27,38,46], the observed CB rate was 79% (95%CI: 75%-82%), while in case series[17,37,43] it was 96% (95%CI: 88% to 99%), and in the single cohort study included[36], 92% (95%CI: 75%-99%). Clinical trials alone exhibited absence of statistically significant heterogeneity and low inconsistency (τ^2 = 0, P = 0.17; I^2 = 38%) (Figure 2B).

Subgroup analysis (number of doses)

Studies that administered more than six doses[17,27,36-38] reported a CB rate of 88% (95%CI: 74%-95%), while the sole study that administered six doses or fewer[43] reported 100% CB (95%CI: 72%-100%) (Figure 2C).

LR

Eighteen studies[17,27-30,32,34-39,41,42,44,47-49], comprising 744 patients, evaluated LR rates in patients with GCTB treated with denosumab. The pooled findings demonstrated a LR rate of 26% (95%CI: 20%-32%); however, significant heterogeneity (τ^2 = 0.2780; P < 0.01) and moderate inconsistency (I^2 = 60%) were observed (Figure 2D).

Sensitivity analysis

When analyzing only case-control studies[29,39,47], the rate of LR was 35% (95%CI: 27%-44%), while in cohorts[28,30,32,36,48] it was 24% (95%CI: 12% to 42%); in the single clinical trial included[29], 15% (95%CI: 09%-22%); in case series[17,34,35,37,41,42,44,49], 23% (95%CI: 19%-28%); and in a non-randomized controlled trial[38], 67% (95%CI: 22% to -96%). Analysis of cohort studies alone demonstrated significant heterogeneity (τ^2 = 0.6420, P = 0.01) and moderate to high inconsistency (I^2 = 68%). Case series showed no statistically significant heterogeneity (τ^2 = 0.0003, P = 0.14), as well as low inconsistency (I^2 = 36%), while the case-control studies were perfectly homogeneous in their results (τ^2 = 0, P = 0.42, I^2 = 0%) (Figure 2E).

Subgroup analysis (number of doses)

In those studies, in which more than six doses of denosumab were administered[17,27,36-38], LR was observed in 23% of cases (95%CI: 17%-31%). In studies that administered six or fewer doses[28,29,32,39,41,42,44], a higher frequency was observed, with LR in 30% of cases (95%CI: 21%-41%). Both groups showed significant heterogeneity and moderate inconsistency (P < 0.10 and I^2 > 50%) (Figure 2F).

IR

Nine studies[26,28,29,36,37,43,46,48,50], comprising 209 patients, evaluated IR rates in patients with GCTB treated with denosumab. The pooled findings demonstrated a response rate of 85% (95%CI: 75%-92%), with statistically significant heterogeneity (τ^2 = 0.5226, P = 0.05), but low heterogeneity (I^2 = 48%) (Figure 2G).

Sensitivity analysis

Across the included case series (three studies, comprising 51 patients)[37,43,50], the IR rate was 94% (95%CI: 83%-98%); these studies presented consistent results and no statistically significant heterogeneity (τ^2 = 0, P = 1; I^2 = 0%). The cohort studies (four articles, comprising 93 participants)[26,28,36,48] reported an IR rate of 74% (95%CI: 60%-84%), with substantial heterogeneity (I^2 = 54%) but low inconsistency (τ^2 = 0.1508, P = 0.09). In the sole clinical trial included[46], the IR rate was 88% (95%CI: 64%-99%), and in the single case-control study[29], 90% (95%CI: 77%-97%) (Figure 2H).

Table 2 Demographic characteristics of the included studies

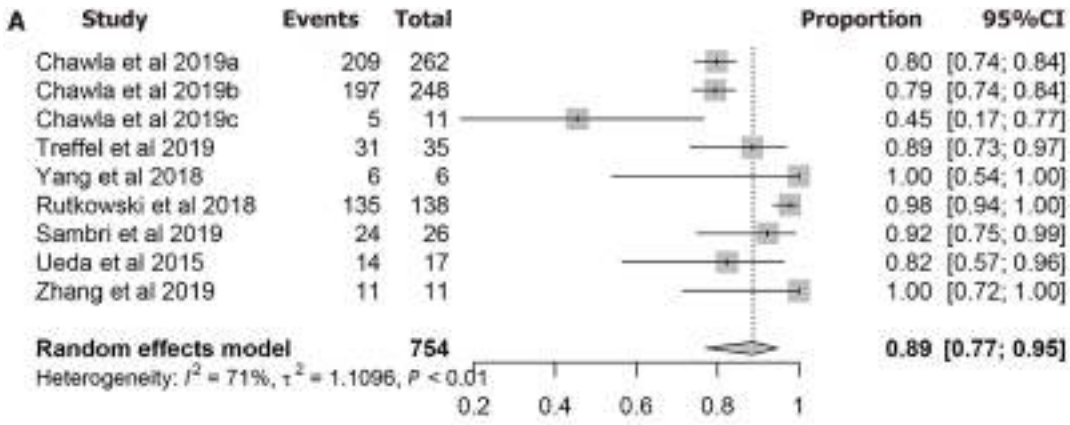
Ref.	Year	Sample	Males	Females	Mean age	Min age	Max age
Agarwal *et al*[39]	2018	54	25	29	32	17	67
Borkowska *et al*[40]	2016	35	14	21	39	19	74
Boye *et al*[33]	2017	18	13	5	39	16	63
Campanacci *et al*[34]	2019	36	16	20	36	18	64
Chawla *et al*[27]	2019a	267	113	154	34	-	-
Chawla *et al*[27]	2019b	253	111	142	34	-	-
Chawla *et al*[27]	2019c	12	7	5	34	-	-
Chinder *et al*[28]	2019	123	87	36	29	-	-
Deveci *et al*[35]	2017	13	5	8	38	26	51
Goldschlager *et al*[50]	2015	5	0	5	36	22	58
Hindiskere *et al*[28]	2020	84	43	41	30	-	-
Latorre *et al*[41]	2021	14	6	8	35	23	46
Lee *et al*[26]	2018	12	-	-	40	21	66
Lim *et al*[30]	2020	68	31	37	34	-	-
Li *et al*[53]	2019	125	49	76	34	-	-
Müller *et al*[49]	2016	25	13	12	35	15	72
Murphy *et al*[48]	2020	154	85	69	35,8	21	51
Puri *et al*[42]	2019	44	26	18	27	13	47
Rutkowski *et al*[17]	2018	138	55	83	39	14	81
Sahito *et al*[32]	2021	70	38	32	30	17	47
Sambri *et al*[36]	2020	26	13	13	47	20	76
Scoccianti *et al*[47]	2018	21	11	10	42	17	66
Treffel *et al*[37]	2020	35	20	15	36	16	72
Ueda *et al*[46]	2015	17	8	9	36	18	66
Yang *et al*[38]	2018	16	6	10	33	16	63
Yi *et al*[45]	2018	8	3	5	37	18	45
Zhang *et al*[43]	2019	11	1	10	38	19	67
Zou *et al*[44]	2019	58	35	23	33	15	67

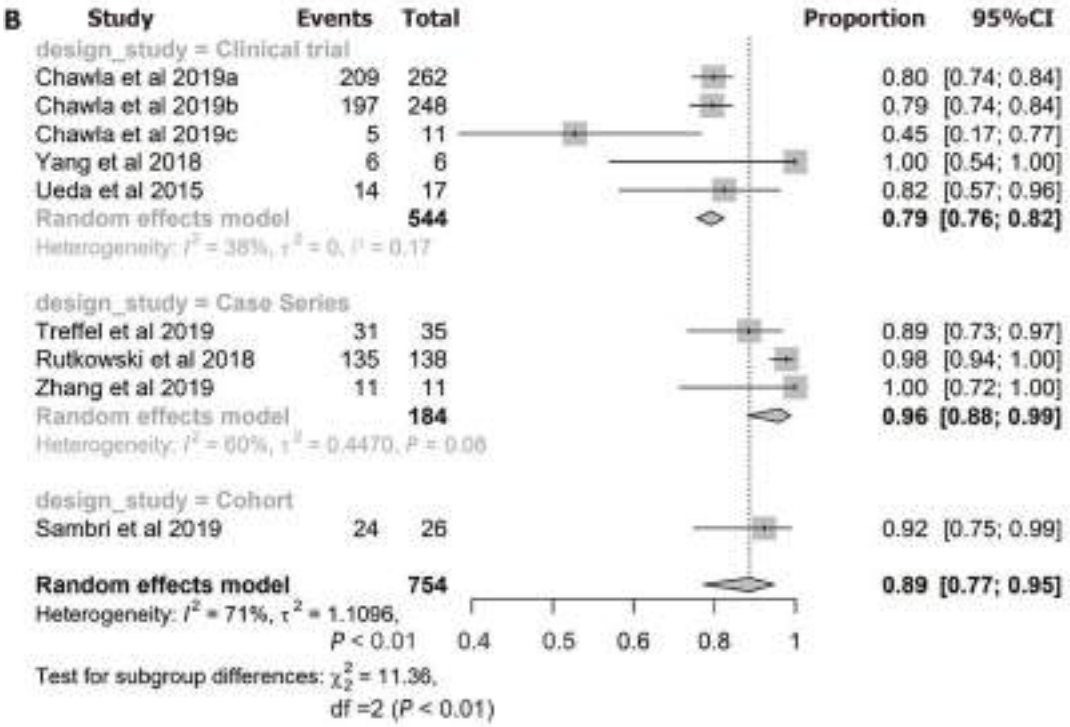
Table 3 Overall demographic characteristics

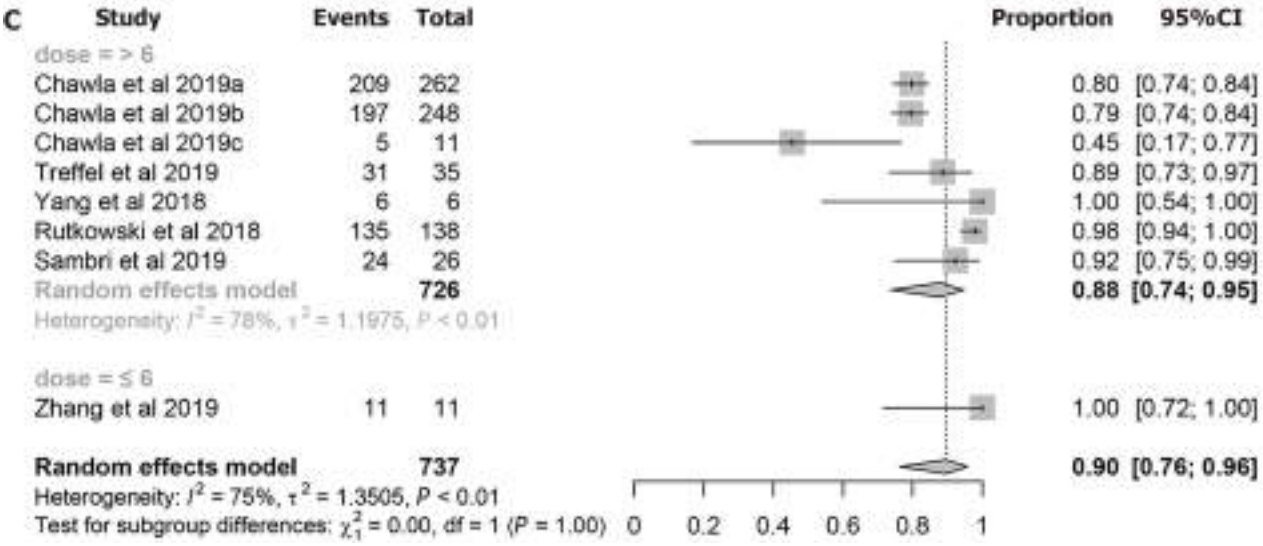
Total participants included across all studies	*n* = 1742
Total males included across all studies	834 (48.2%)
Total females included across all studies	896 (51.8%)
Mean age of participants	35 years
Minimum age of participants	13 years
Maximum age of participants	81 years

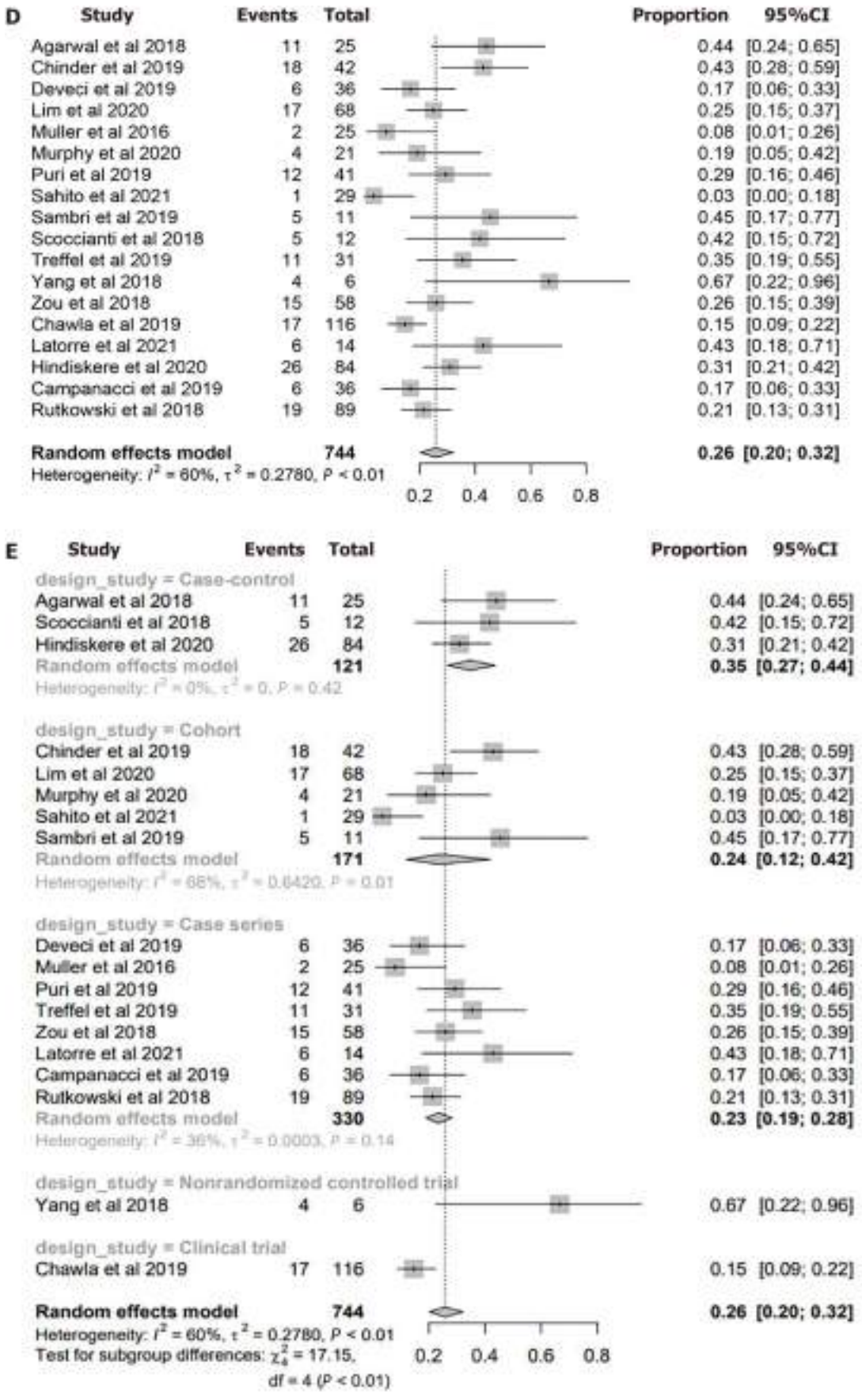
Subgroup analysis (number of doses)

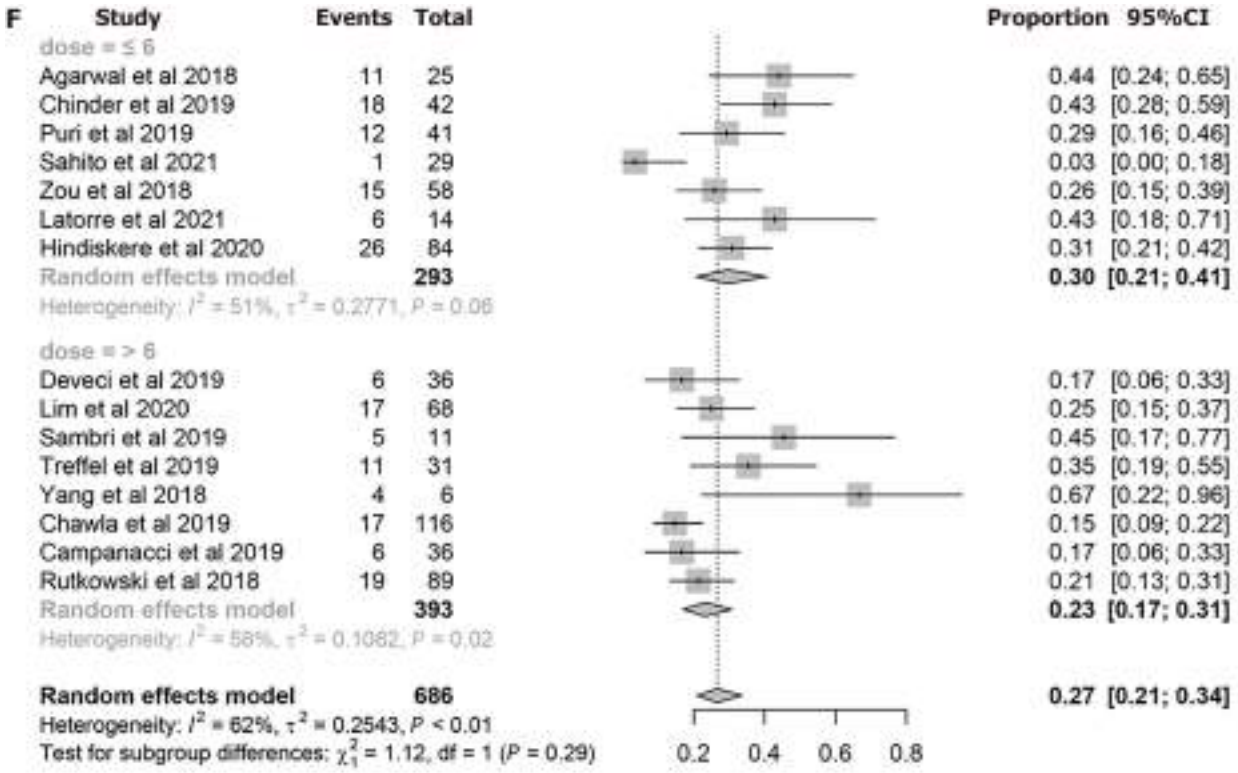
Studies that administered more than six doses of denosumab[36,37] reported an IR rate of 83% (95%CI: 61%-93%); however, they had significant heterogeneity and moderate inconsistency (P = 0.04, I^2 = 77%). Six or fewer doses[28,29,43] were associated with an IR rate of 87% (95%CI: 79%-92%), with consistent results and no significant heterogeneity (P = 0.52, I^2 = 0%) (Figure 2I).

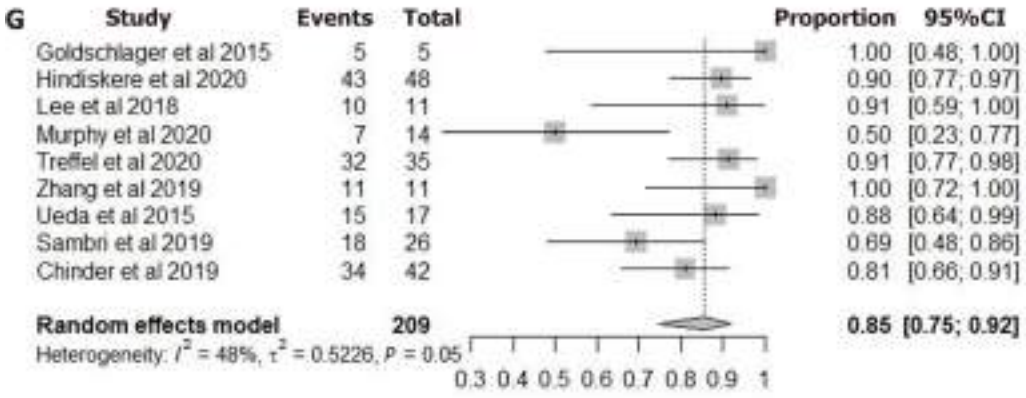

A
Study
Events
Total
Proportion
95%CI
Chawla et al 2019a 209 262 0.80 [0.74; 0.84]
Chawla et al 2019b 197 248 0.79 [0.74; 0.84]
Chawla et al 2019c 5 11 0.45 [0.17; 0.77]
Treffel et al 2019 31 35 0.89 [0.73; 0.97]
Yang et al 2018 6 6 1.00 [0.54; 1.00]
Rutkowski et al 2018 135 138 0.98 [0.94; 1.00]
Sambri et al 2019 24 26 0.92 [0.75; 0.99]
Ueda et al 2015 14 17 0.82 [0.57; 0.96]
Zhang et al 2019 11 11 1.00 [0.72; 1.00]
Random effects model 754 0.89 [0.77; 0.95]
Heterogeneity: I^2 = 71%, τ^2 = 1.1096, P < 0.01
0.2
0.4
0.6
0.8
1

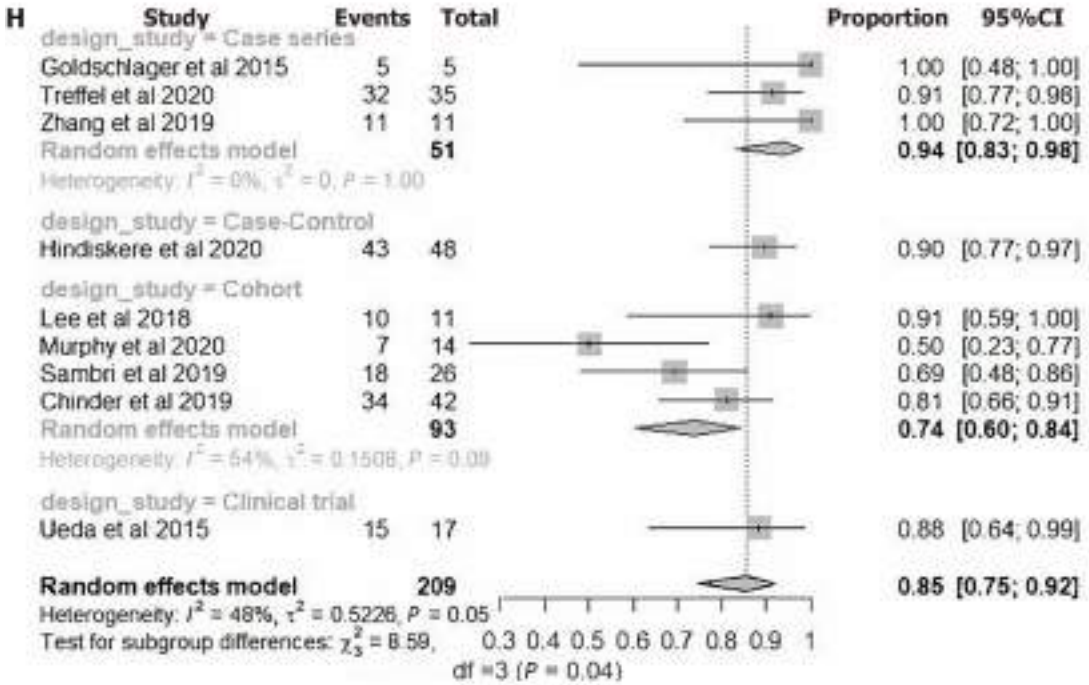

B
Study
Events
Total
Proportion
95%CI
design_study = Clinical trial
Chawla et al 2019a 209 262 0.80 [0.74; 0.84]
Chawla et al 2019b 197 248 0.79 [0.74; 0.84]
Chawla et al 2019c 5 11 0.45 [0.17; 0.77]
Yang et al 2018 6 6 1.00 [0.54; 1.00]
Ueda et al 2015 14 17 0.82 [0.57; 0.96]
Random effects model 544 0.79 [0.76; 0.82]
Heterogeneity: I^2 = 38%, τ^2 = 0, P = 0.17
design_study = Case Series
Treffel et al 2019 31 35 0.89 [0.73; 0.97]
Rutkowski et al 2018 135 138 0.98 [0.94; 1.00]
Zhang et al 2019 11 11 1.00 [0.72; 1.00]
Random effects model 184 0.96 [0.88; 0.99]
Heterogeneity: I^2 = 60%, τ^2 = 0.4470, P = 0.08
design_study = Cohort
Sambri et al 2019 24 26 0.92 [0.75; 0.99]
Random effects model 754 0.89 [0.77; 0.95]
Heterogeneity: I^2 = 71%, τ^2 = 1.1096, P < 0.01
0.4
0.5
0.6
0.8
1
Test for subgroup differences: χ^2_2 = 11.36, df =2 (P < 0.01)


C
Study
Events
Total
Proportion
95%CI
dose = > 6
Chawla et al 2019a 209 262 0.80 [0.74; 0.84]
Chawla et al 2019b 197 248 0.79 [0.74; 0.84]
Chawla et al 2019c 5 11 0.45 [0.17; 0.77]
Treffel et al 2019 31 35 0.89 [0.73; 0.97]
Yang et al 2018 6 6 1.00 [0.54; 1.00]
Rutkowski et al 2018 135 138 0.98 [0.94; 1.00]
Sambri et al 2019 24 26 0.92 [0.75; 0.99]
Random effects model 726 0.88 [0.74; 0.95]
Heterogeneity: I^2 = 78%, τ^2 = 1.1975, P < 0.01
dose = ≤ 6
Zhang et al 2019 11 11 1.00 [0.72; 1.00]
Random effects model 737 0.90 [0.76; 0.96]
Heterogeneity: I^2 = 75%, τ^2 = 1.3505, P < 0.01
Test for subgroup differences: χ^2_1 = 0.00, df = 1 (P = 1.00)
0
0.2
0.4
0.6
0.8
1


D
Study
Events
Total
Proportion
95%CI
Agarwal et al 2018 11 25 0.44 [0.24; 0.65]
Chinder et al 2019 18 42 0.43 [0.28; 0.59]
Deveci et al 2019 6 36 0.17 [0.06; 0.33]
Lim et al 2020 17 68 0.25 [0.15; 0.37]
Muller et al 2016 2 25 0.08 [0.01; 0.26]
Murphy et al 2020 4 21 0.19 [0.05; 0.42]
Puri et al 2019 12 41 0.29 [0.16; 0.46]
Sahito et al 2021 1 29 0.03 [0.00; 0.18]
Sambri et al 2019 5 11 0.45 [0.17; 0.77]
Scoccianti et al 2018 5 12 0.42 [0.15; 0.72]
Treffel et al 2019 11 31 0.35 [0.19; 0.55]
Yang et al 2018 4 6 0.67 [0.22; 0.96]
Zou et al 2018 15 58 0.26 [0.15; 0.39]
Chawla et al 2019 17 116 0.15 [0.09; 0.22]
Latorre et al 2021 6 14 0.43 [0.18; 0.71]
Hindiskere et al 2020 26 84 0.31 [0.21; 0.42]
Campanacci et al 2019 6 36 0.17 [0.06; 0.33]
Rutkowski et al 2018 19 89 0.21 [0.13; 0.31]
Random effects model 744 0.26 [0.20; 0.32]
Heterogeneity: I^2 = 60%, τ^2 = 0.2780, P < 0.01
0.2
0.4
0.6
0.8
E
Study
Events
Total
Proportion
95%CI
design_study = Case-control
Agarwal et al 2018 11 25 0.44 [0.24; 0.65]
Scoccianti et al 2018 5 12 0.42 [0.15; 0.72]
Hindiskere et al 2020 26 84 0.31 [0.21; 0.42]
Random effects model 121 0.35 [0.27; 0.44]
Heterogeneity: I^2 = 0%, τ^2 = 0, P = 0.42
design_study = Cohort
Chinder et al 2019 18 42 0.43 [0.28; 0.59]
Lim et al 2020 17 68 0.25 [0.15; 0.37]
Murphy et al 2020 4 21 0.19 [0.05; 0.42]
Sahito et al 2021 1 29 0.03 [0.00; 0.18]
Sambri et al 2019 5 11 0.45 [0.17; 0.77]
Random effects model 171 0.24 [0.12; 0.42]
Heterogeneity: I^2 = 68%, τ^2 = 0.6420, P = 0.01
design_study = Case series
Deveci et al 2019 6 36 0.17 [0.06; 0.33]
Muller et al 2016 2 25 0.08 [0.01; 0.26]
Puri et al 2019 12 41 0.29 [0.16; 0.46]
Treffel et al 2019 11 31 0.35 [0.19; 0.55]
Zou et al 2018 15 58 0.26 [0.15; 0.39]
Latorre et al 2021 6 14 0.43 [0.18; 0.71]
Campanacci et al 2019 6 36 0.17 [0.06; 0.33]
Rutkowski et al 2018 19 89 0.21 [0.13; 0.31]
Random effects model 330 0.23 [0.19; 0.28]
Heterogeneity: I^2 = 36%, τ^2 = 0.0003, P = 0.14
design_study = Nonrandomized controlled trial
Yang et al 2018 4 6 0.67 [0.22; 0.96]
design_study = Clinical trial
Chawla et al 2019 17 116 0.15 [0.09; 0.22]
Random effects model 744 0.26 [0.20; 0.32]
Heterogeneity: I^2 = 60%, τ^2 = 0.2780, P < 0.01
Test for subgroup differences: χ^2_4 = 17.15, df = 4 (P < 0.01)
0.2
0.4
0.6
0.8


F
Study
Events
Total
Proportion
95%CI
dose = ≤ 6
Agarwal et al 2018 11 25 0.44 [0.24; 0.65]
Chinder et al 2019 18 42 0.43 [0.28; 0.59]
Puri et al 2019 12 41 0.29 [0.16; 0.46]
Sahito et al 2021 1 29 0.03 [0.00; 0.18]
Zou et al 2018 15 58 0.26 [0.15; 0.39]
Latorre et al 2021 6 14 0.43 [0.18; 0.71]
Hindiskere et al 2020 26 84 0.31 [0.21; 0.42]
Random effects model 293 0.30 [0.21; 0.41]
Heterogeneity: I^2 = 51%, τ^2 = 0.2771, P = 0.06
dose = > 6
Deveci et al 2019 6 36 0.17 [0.06; 0.33]
Lim et al 2020 17 68 0.25 [0.15; 0.37]
Sambri et al 2019 5 11 0.45 [0.17; 0.77]
Treffel et al 2019 11 31 0.35 [0.19; 0.55]
Yang et al 2018 4 6 0.67 [0.22; 0.96]
Chawla et al 2019 17 116 0.15 [0.09; 0.22]
Campanacci et al 2019 6 36 0.17 [0.06; 0.33]
Rutkowski et al 2018 19 89 0.21 [0.13; 0.31]
Random effects model 393 0.23 [0.17; 0.31]
Heterogeneity: I^2 = 58%, τ^2 = 0.1082, P = 0.02
Random effects model 686 0.27 [0.21; 0.34]
Heterogeneity: I^2 = 62%, τ^2 = 0.2543, P < 0.01
Test for subgroup differences: χ^2_1 = 1.12, df = 1 (P = 0.29)
0.2 0.4 0.6 0.8


G
Study
Events
Total
Proportion
95%CI
Goldschlager et al 2015 5 5 1.00 [0.48; 1.00]
Hindiskere et al 2020 43 48 0.90 [0.77; 0.97]
Lee et al 2018 10 11 0.91 [0.59; 1.00]
Murphy et al 2020 7 14 0.50 [0.23; 0.77]
Treffel et al 2020 32 35 0.91 [0.77; 0.98]
Zhang et al 2019 11 11 1.00 [0.72; 1.00]
Ueda et al 2015 15 17 0.88 [0.64; 0.99]
Sambri et al 2019 18 26 0.69 [0.48; 0.86]
Chinder et al 2019 34 42 0.81 [0.66; 0.91]
Random effects model 209 0.85 [0.75; 0.92]
Heterogeneity: I^2 = 48%, τ^2 = 0.5226, P = 0.05
0.3 0.4 0.5 0.6 0.7 0.8 0.9 1


H
Study
Events
Total
Proportion
95%CI
design_study = Case series
Goldschlager et al 2015 5 5 1.00 [0.48; 1.00]
Treffel et al 2020 32 35 0.91 [0.77; 0.98]
Zhang et al 2019 11 11 1.00 [0.72; 1.00]
Random effects model 51 0.94 [0.83; 0.98]
Heterogeneity: I^2 = 0%, τ^2 = 0, P = 1.00
design_study = Case-Control
Hindiskere et al 2020 43 48 0.90 [0.77; 0.97]
design_study = Cohort
Lee et al 2018 10 11 0.91 [0.59; 1.00]
Murphy et al 2020 7 14 0.50 [0.23; 0.77]
Sambri et al 2019 18 26 0.69 [0.48; 0.86]
Chinder et al 2019 34 42 0.81 [0.66; 0.91]
Random effects model 93 0.74 [0.60; 0.84]
Heterogeneity: I^2 = 64%, τ^2 = 0.1508, P = 0.03
design_study = Clinical trial
Ueda et al 2015 15 17 0.88 [0.64; 0.99]
Random effects model 209 0.85 [0.75; 0.92]
Heterogeneity: I^2 = 48%, τ^2 = 0.5226, P = 0.05
Test for subgroup differences: χ^2_3 = 8.59, df = 3 (P = 0.04)
0.3 0.4 0.5 0.6 0.7 0.8 0.9 1

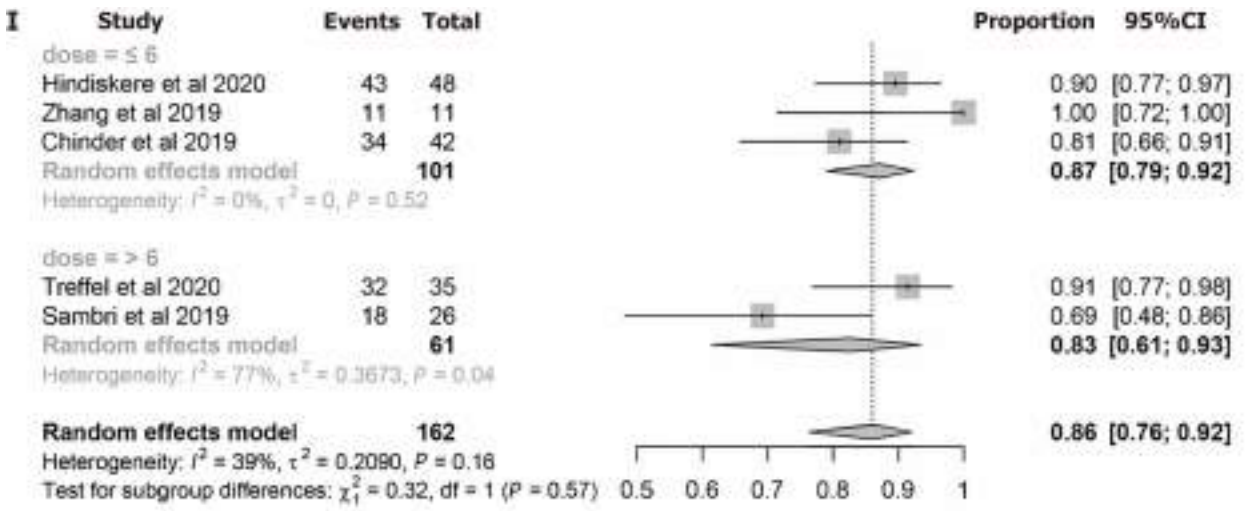


Figure 2 Random-effects model. A: Calculation of clinical benefit rates with denosumab therapy; B: Sensitivity analysis by methodological design of studies that evaluated clinical benefit; C: Subgroup analysis (number of doses) of studies that evaluated clinical benefit; D: Calculation of local recurrence rates with denosumab therapy; E: Sensitivity analysis by methodological design of studies that evaluated local recurrence; F: Subgroup analysis (number of doses) of studies that evaluated local recurrence; G: Calculation of imaging response rates with denosumab therapy; H: Sensitivity analysis by methodological design of studies that evaluated imaging response; I: Subgroup analysis(number of doses) of studies that evaluated imaging response.

AE

Hypocalcemia was the AE most commonly reported across the included studies. Eight articles[17,31,34-37,39,46], including a total of 425 patients, reported a 6% frequency of hypocalcemia (95%CI: 4%-9%), with no heterogeneity identified across these studies ($\tau^2 = 0$, $I^2 = 0\%$; $P = 0.82$). The three most frequent AE were, respectively: Back pain, 26% (95%CI: 18%-37%); fatigue, 25% (95%CI: 20%-30%); and extremity pain, 24% (95%CI: 19%-30%). Osteonecrosis of the jaw was reported in five studies[17,27,33,35,37] (830 participants), for a frequency of 4% (95%CI: 2%-7%). Sambri *et al*[36] reported a single case of malignant transformation to osteosarcoma among 26 patients with GCTB treated with denosumab (Supplementary Table 3).

DISCUSSION

GCTB is a common bone neoplasm, accounting for approximately 20% of all primary bone tumors[14]. It preferentially affects young individuals in the most productive years of life and is highly locally aggressive, with high recurrence rates and potential for metastatic spread to the lungs; it is currently classified as an intermediate variant (locally aggressive, rarely metastasizing) of the category of osteoclastic giant cell-rich tumors[51].

The standard treatment for GCTB is surgical, consisting of intralesional curettage or *en bloc* resection. Wide resection provides the best outcomes in terms of preventing LR, but is often associated with local morbidity and is not always feasible (some tumors are unresectable).

The advent of denosumab has changed the clinical course of GCTB and the therapeutic approach to this neoplasm[43]. Denosumab has been used as neoadjuvant therapy in patients with locally advanced GCTB, with the aim of downstaging lesions to facilitate tumor resection; it also allows local control of unresectable tumors and treatment of metastases[3].

However, there is no consensus in the literature regarding the optimal denosumab regimen for GCTB, particularly concerning the number of doses (duration of therapy). Some authors advocate the administration of more than six doses, while others advocate six or fewer[18,46].

The efficacy of these different treatment regimens in patients with GCTB has not yet been widely investigated; to the best of our knowledge, no systematic review or meta-analysis has been conducted in this context. The present study was designed to evaluate the efficacy of different denosumab-containing treatment regimens in patients with GCTB in terms of CB, IR, LR, and AE.

The rate of LR after surgical treatment of GCTB without denosumab ranges from 15% to 45%[4,18]. In our review, we found a mean LR of 26% with adjunctive denosumab, ranging from 3.45%[32] to 66.7%[38]. This significant heterogeneity can be explained by population selection, type of surgery, and site and stage of the primary tumor. Yang *et al*[38] compared the outcomes of treating stage 3 sacral GCTBs with preoperative embolization and curettage with a high-speed bur with or without neoadjuvant denosumab. The group not treated with denosumab had zero LR, while those cases treated with denosumab (more than six doses) relapsed in 66.7% of cases, a fact attributed by the authors to (1) The permanence of tumor cells in the newly formed bone induced by denosumab after cessation of treatment; and (2) cortical thickening and formation of new bone matrix, which both made curettage difficult and prevented the surgeon from delineating the true extent of the tumor. Sahito *et al*[32] enrolled patients with grade III GCTB located mainly in the long bones, divided into two groups: One was pre-treated with denosumab (three or four weekly 120 mg doses) and the other received no neoadjuvant treatment. The denosumab-treated group had a recurrence rate of 3.45%, while the untreated

group had a recurrence rate of 4.88%.

Regarding study designs, we found homogeneity in the results of case-control studies[29,39,47], which reported a relatively high rate of LR (35%), explained, among other factors, by the type of surgery performed–two of the three studies evaluated cases treated by curettage, with 44%[39] and 42%[47] LR rates, while the other[29] evaluated patients undergoing curettage with *en bloc* resection and reported a LR rate of 31%. When considering only those patients treated by curettage, the rate of LR was 36%. Among studies that used denosumab regimens consisting of six or fewer doses, the overall LR rate was 30%[28,29,32,39,41,42,44], *vs* 21% which administered six doses or more[17,27,30,34-38]. We did not find a statistically significant difference in LR between these studies, regardless of dosage (χ^2 = 2.38, P = 0.30). The incidence of LR appears to be associated with the affected site (sacrum, distal radius, short bones of the feet and hands) and the type of surgery performed (more frequent with curettage than with *en bloc* resection).

Some studies defined CB as a composite of patient-reported pain reduction, improved function, and improved mobility, while others analyzed these outcomes separately. The seven articles that evaluated this item as a composite outcome reported an average CB rate of 89%. In two of the studies[38,43] 100% benefit was observed, but these had a small sample size (six and 11 participants, respectively); Yang *et al*[38] adopted a treatment regimen consisting of more than six doses, while Zhang *et al*[43] administered six doses or fewer. Cohort 3 of a phase II open-label trial by Chawla *et al*[27], reported the lowest overall rate of CB (45%), much lower than other articles and cohorts 1 and 2 of the same study; this fact was attributed to the selection of participants, who all had unresectable GCTBs.

The main radiographic feature of GCTB is an osteolytic pattern secondary to bone resorption. The imaging modalities most commonly used in the diagnosis and follow-up of patients with this tumor are plain radiography, computed tomography, magnetic resonance imaging, positron emission tomography and computed tomography (PET-CT). IR after denosumab treatment is evaluated through such scans, seeking to identify a reduction in the size (diameter) of the lesion, improvement or resolution of osteolysis (ossification of the lesion), calcification of tumor margins, or reduction of the maximum standardized uptake value (SUVmax) on PET-CT. There was no single criterion across all studies regarding assessment of IR; however, some parameters were common to most of the included investigations (reduction, stabilization, or progression of tumor size; ossification of the bone matrix; calcification of tumor margins).

Of the nine studies that evaluated IR[26,28,29,36,37,43,46,48,50], seven reported an excellent response (> 80%)[26,28,29,37,43,46,50]. Diverging from other studies, Murphy *et al*[48] reported an IR rate of 50%, as they considered reduction in lesion size (20.3%) as the sole criterion for assessment. Goldschlager *et al*[50] also used reduction in tumor size as their sole criterion and reported a 100% response rate; in this study, however, only patients with GCTBs restricted to the spine were included. Most studies (seven) used more than one criterion to evaluate IR[26,28,29,36,37,43,46]. Among these, the most common schemes used were the MD Anderson Cancer Center Bone Response Criteria and the Choi inverse criteria. Regarding the number of doses, three studies[28,29,43] used six doses or fewer and obtained a pooled IR rate of 87%. Sambri *et al*[36] and Treffel *et al*[37] administered more than six doses and obtained an 83% IR rate; this difference was not statistically significant (χ^2 = 0.32, P = 0.57). However, we observed a better response in absolute figures with fewer doses, suggesting that GCTBs respond well to denosumab, with IR being achieved after just a few doses.

Overall, the literature pertaining to the use of denosumab and its regimens in the treatment of GCTB remains controversial, especially regarding the duration of treatment. In some studies, treatment was discontinued after a subjective analysis regarding patient response and surgical indication at that time; in others, a predefined protocol was followed regardless of the response obtained with neoadjuvant treatment.

He *et al*[52] indicated possible safety concerns regarding the use of denosumab, specifically regarding an elevated likelihood of experiencing osteonecrosis of the jaw, arthralgia, pain in the extremities, back pain, myalgia, and bone pain events, findings which underscore the critical importance of pharmacovigilance and are consistent with established clinical observations. In our study, the most frequent AE associated with the use of denosumab were back pain (26%), fatigue (25%), and pain in the extremities (24%)[17,31,34-37,40,46]. Osteonecrosis of the jaw has been reported at a frequency of 4%[17,27,33,35,37]. Hypocalcemia was the most reported AE in the included studies. Only one case of malignant transformation to osteosarcoma has been reported[36,53].

This review has some limitations. Among them, the quality of the included studies – only four were clinical trials, and of these, only one was randomized – poses a risk of selection bias. The homogeneity of the population included across the selected studies is debatable, especially regarding lesion status (first operation or LR) and type of surgical treatment (curettage or wide resection). There was no uniformity whatsoever in the inclusion and exclusion criteria used by the authors in the studies. Publication bias– *i.e.*, the greater likelihood of studies being published if results are positive–must also be considered when interpreting the results, although this was mitigated by the fact that we carried out a comprehensive search of several databases, including the gray literature, in three different languages.

CONCLUSION

This systematic review with meta-analysis confirms the efficacy of denosumab in reducing pain and improving function and mobility in GCTB. Patients obtained high CB rates with this treatment; IR rates were also high and consistent, up to 100% in some studies. However, there was no statistically significant difference in efficacy among the different denosumab regimens adopted, especially regarding the number of doses. The LR rate is relatively high overall, regardless of the number of doses administered, but similar to that seen in individuals who do not receive neoadjuvant denosumab. It tends to be higher in those cases treated with curettage and lower in patients undergoing *en bloc* resection, again regardless of the number of doses administered. Several AE were reported; most were mild, except for a single case of malignant transformation to osteosarcoma.

FOOTNOTES

Author contributions: Barreto BG contributed to the design and conception of the study and the writing of the manuscript; Moreira FD and Paz CLD contributed to acquisition of data and statistical analyses; Barreto BG and Guedes A contributed to the performance and quality of the research; Guedes A and Santili C contributed to final revision and the writing of the manuscript.

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