Safety of denosumab versus zoledronic acid in patients with bone-related diseases: a systematic review and meta-analysis

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Abstract

Introduction: The aim of the study was to compare the safety of denosumab (Dmab) versus zoledronic acid (ZA) in patients with bone-related diseases. Both Dmab and ZA have been widely used in the treatment of bone-related diseases, but which drug is an optimal treatment in terms of safety remains controversial.

Material and methods: PubMed, Embase, Web of Science, the Cochrane Central Library, and ClinicalTrials.gov were systematically searched up to 1st January 2021, and were evaluated by Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. Randomized controlled trials comparing relevant outcomes of Dmab versus ZA in patients with bone-related diseases were included.

Results: A total of 13 studies involving 21,042 participants were included. The incidence of total adverse events was significantly lower in patients receiving Dmab treatment than in those undergoing ZA treatment (OR = 0.84, 95% CI: 0.75–0.94, p = 0.003). Nine trials comparing Dmab with ZA further indicated that Dmab was significantly better than ZA in controlling the incidence of serious adverse events (OR = 0.91, 95% CI: 0.85–0.99, p = 0.02). Compared to ZA, Dmab administration was correlated with a lower risk of skeletal-related events (OR = 0.77, 95% CI: 0.70–0.85, p = 0.00001). However, no significant difference was found in the rate of infection events between Dmab and ZA (OR = 1.06, 95% CI: 0.93–1.20, p = 0.39).

Conclusions: This study demonstrated superiority of Dmab over ZA in treating bone-related diseases in terms of safety.

Key words: denosumab, zoledronic acid, bone-related diseases, adverse events.

Introduction

With the increase of tumor incidence and the aging of the population, the prevalence of bone-related diseases along with the demand for corresponding medications is growing. We attached great importance to bone-related diseases [1–3]. As two potent antiresorptive

agents, both denosumab (Dmab) and zoledronic acid (ZA) [4] have been widely used in the treatment of bone-related diseases, including but not limited to osteoporosis [5, 6], bone metastases secondary to solid tumors [7–9], multiple myeloma [10, 11] and giant cell tumor of bone [12, 13]. As a potent intravenous bisphosphonate, ZA plays a critical role in the prevention of skeletal complications in bone-related diseases [5, 14]. Denosumab is a fully human monoclonal antibody of the immunoglobulin G2 isotype, which functions against the receptor activator of nuclear factor κB ligand (RANKL) and thereby inhibits osteoclast activation and function [15], and its use is significantly less limited to renal toxicity [16]. Growing evidence suggests that Dmab is superior in terms of efficacy [17, 18], safety [5] and even cost-effectiveness [19, 20] over ZA. Published meta-analyses comparing the efficacy between Dmab and ZA for treatment of bone metastases in patients with solid tumors demonstrated that Dmab was better than ZA in preventing complications and delaying the onset of skeletal-related events (SREs) [21–23]. However, meta-analyses evaluating the safety between Dmab and ZA are still insufficient. In the few studies evaluating this, the use of both drugs was confined to the treatment of patients with bone metastases [16, 21, 23]. With the continuous expansion of indications of both drugs and increased interest in identifying the optimal treatment for bone-related diseases, it is necessary to comprehensively compare the safety of Dmab and ZA based on a wide range of bone-related diseases, which is also an important aspect to guide the clinical medication. Therefore, in this study, we conducted a systematic review and meta-analysis based on clinical trials to compare the safety and efficacy between Dmab and ZA in patients with bone-related diseases.

Material and methods

Registration of this systematic review has been completed on the PROSPERO (International Prospective Register of Systematic Reviews) website, under the registration number CRD42021227328. This systematic review was conducted with adherence to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [24].

Study selections

Relevant studies were searched and identified by individually searching the following databases: PubMed, Embase, Web of Science, the Cochrane Central Library, and ClinicalTrials.gov up to 1st January 2021. For all databases, the following key terms were used for searching: "denosumab", "zoledronic acid" and "bone". The study design was limited to randomized controlled trials (RCTs). This meta-analysis adhered to the Critical Appraisal Skills Programme (CASP) Checklist. Eligibility assessment was performed by two independent reviewers (L.W.H. and J.R.Y.). Disagreements between reviewers were resolved by group discussion and consensus.

Inclusion and exclusion criteria

Eligibility was assessed by two independent reviewers (L.W.H. and J.R.Y.), with consensus reached by discussing conflicts with a third investigator (L.Y.). Assessments were performed and repeated twice. Only RCTs were included. First, the titles and abstracts were assessed. Full texts of potentially qualified studies were then obtained and carefully reviewed. Reviewers were not blinded to the authorship of the studies. Dissertations, conference proceedings, and studies in non-English languages were excluded.

Outcomes of interest

The primary outcome measure was the rate of adverse events. The secondary outcome measures were the rates of serious adverse events, SREs and infection events.

Data collection

The following data were extracted: first author, year of study, country of origin, study population, number of patients, basic demographic characteristics, treatment information and data of outcomes of interest. The data were extracted and cross-checked independently by two authors (L.W.H. and J.R.Y.). Disagreements were resolved through deep discussion with a third reviewer (L.Y.) until we reached a consensus.

Evaluation of quality of evidence

The methodological quality of the selected studies was blindly evaluated by two independent reviewers (L.W.H. and J.R.Y.). Disagreements were discussed among the group and resolved by a third assessor (L.Y.). The study quality was assessed using the CASP Checklist (Table I), which evaluates the risk of bias and comprises 11 items related to methodological quality and statistical reporting. Discrepancies and disagreements were resolved by consensus.

Statistical analysis

Data analyses were performed using the Cochrane Collaboration's Review Manager program (RevMan version 5.3; Cochrane Collaboration,

Table I. Critical Appraisal Skills Programme (CASP) Checklist

Item number	Items of quality assessment
1	Was the assigned treatment adequately concealed before allocation?
2	Were the outcome of patients who withdrew described and included in the analysis (intention to treat)?
3	Were the outcome assessors blinded to the treatment status?
4	Were the treatment and control groups comparable at entry?
5	Were the participants blinded to the assignment status after allocation?
6	Were the treatment providers blind to the assignment status?
7	Were the care programs, other than the trial options, identical?
8	Were the inclusion and exclusion criteria clearly defined?
9	Were the interventions clearly defined?
10	Were the outcome measures used clearly defined?
11	Were diagnostic tests used in the outcome assessment clinically useful?

Oxford, UK). Meta-analysis was conducted to calculate pooled odds ratios (ORs) with 95% confidence intervals (CIs). We evaluated heterogeneity across studies using the Cochrane chi-square (χ^2) test and quantified it with the I^2 statistic [25]. I^2 values of 25%, 50% and 75% represented low, moderate and high heterogeneity, respectively [26]. Fixed-effects or random-effects models were used accordingly. The publication bias was detected by funnel plots and was statistically examined by Egger's test [27]. Egger's test was performed in STATA version 16 (StataCorp, College Station, TX).

Results

Literature search

A flow diagram of the literature search is shown in Figure 1. Among 565 potentially eligible articles, 13 fulfilled the inclusion criteria. Initially, through the electronic database search, we identified 565 citations. Examinations of the reference lists in all relevant papers, recent editorials, and related review articles yielded no further studies for evaluation. Non-RCTs were excluded and the remaining 26 articles were then selected after reading the titles and abstracts. After reading the full texts, 13 studies were further excluded because they did not report relevant outcomes. The remaining 13 RCTs met our inclusion criteria and were ultimately included in the qualitative analysis and final meta-analysis.

Study characteristics

The characteristics of enrolled RCTs were presented in Table II. Our meta-analysis included 21,042 patients (10,073 men and 10,969 women) who were diagnosed with bone-related disease from six different countries. Among them, 10,535 (50.1%) patients were treated with Dmab and 10,507 (49.9%) patients were treated with ZA.

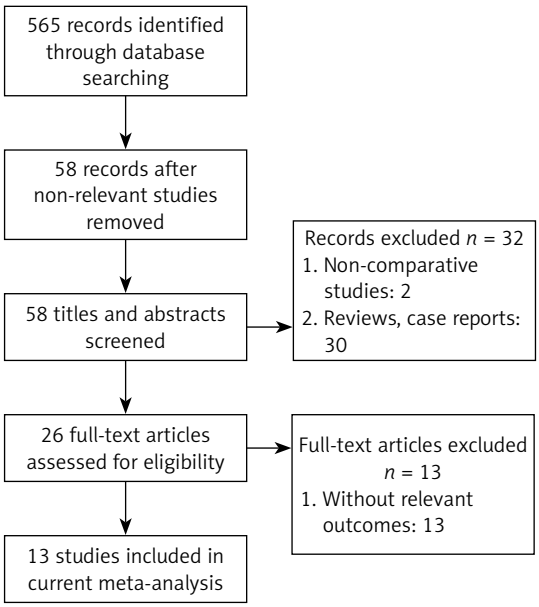

Figure 1. Flow diagram of the literature search

The results of the quality assessment of the included RCTs are detailed in Table III.

Primary outcome

Adverse events

Ten of the included studies reported the overall rate of adverse events. The adverse events rate was 86.3% (6581/7623) in the Dmab group and 87.6% (6644/7584) in the ZA group (OR = 0.84, 95% CI: 0.75–0.94, p = 0.003) (Figure 2).

Secondary outcomes

Serious adverse events

Nine RCTs reported relevant data regarding the rate of serious adverse events. The incidence of serious adverse events was significantly lower in the Dmab group compared with the ZA group (OR = 0.91, 95% CI: 0.85–0.99, p = 0.02) (Figure 3).

Table II. Characteristics of randomized controlled trials enrolled in the meta-analysis

Year	Country	Design	D group			Z group		
			Patients number	Median age	Male percentage	Patients number	Median age	Male percentage
2010	America	RCT	1026	57	0.8	1020	56	0.9
2011	America	RCT	886	60	66.0	890	61	62.0
2011	France	RCT	950	71	100.0	951	71	100.0
2012	Italy	RCT	411	60	74.0	400	61	68.0
2012	America	RCT	886	60	66.0	890	61	62.0
2012	Spain	RCT	1026	57	0.8	1020	56	0.9
2014	America	RCT	800	59	66.0	797	61	62.0
2015	France	RCT	950	71	100.0	951	71	100.0
2015	Germany	RCT	1912	58	31.0	1910	59	29.0
2016	America	RCT	321	68.5	0.0	322	69.5	0.0
2018	America	RCT	859	63	54.0	859	63	55.0
2018	Greece	RCT	30	64.8	0.0	27	65.2	0.0
2016	America	RCT	325	56	0.0	342	55.9	0.0
			153	70	100.0	128	71	100.0

Additions for Table II

References	Year	Country	Design	D group intervention	Z group intervention
Stopeck, Alison T.	2010	America	RCT	120 mg q4w s.c.	4 mg q4w ivgtt
Henry, David H.	2011	America	RCT	120 mg q4w s.c.	4 mg q4w ivgtt
Fizazi, Karim	2011	France	RCT	120 mg q4w s.c.	4 mg q4w ivgtt
Scagliotti, Giorgio Vittorio	2012	Italy	RCT	120 mg q4w s.c.	4 mg q4w ivgtt
Vadhan-Raj, Saroj	2012	America	RCT	120 mg q4w s.c.	4 mg q4w ivgtt
Martin, Miguel	2012	Spain	RCT	120 mg q4w s.c.	4 mg q4w ivgtt
Henry, David	2014	America	RCT	120 mg q4w s.c.	4 mg q4w ivgtt
Smith, Matthew R.	2015	France	RCT	120 mg q4w s.c.	4 mg q4w ivgtt
Diel, Ingo J.	2015	Germany	RCT	120 mg q4w s.c.	4 mg q4w ivgtt
Miller, Paul D.	2016	America	RCT	60 mg q6m twice, s.c.	5 mg once ivgtt
Raje, Noopur	2018	America	RCT	120 mg q4w s.c.	4 mg q4w ivgtt
Anastasilakis, Athanasios D.	2018	Greece	RCT	60 mg q6m twice, s.c.	5 mg once ivgtt
Stopeck, Alison T.	2016	America	RCT	120 mg q4w s.c.	4 mg q4w ivgtt
				120 mg q4w s.c.	4 mg q4w ivgtt

Year	Country	Design	Primary disease
2010	America	RCT	Advanced breast cancer with bone metastases
2011	America	RCT	Advanced cancer or multiple myeloma with bone metastases
2011	France	RCT	Castration-resistant prostate cancer with bone metastases
2012	Italy	RCT	Lung cancer with bone metastases
2012	America	RCT	Advanced cancer or multiple myeloma with bone metastases
2012	Spain	RCT	Advanced breast cancer
2014	America	RCT	Advanced solid tumor with bone metastases
2015	France	RCT	Castration-resistant prostate cancer with bone metastases
2015	Germany	RCT	Advanced breast cancer and other solid tumors (excluding breast or prostate cancer) or multiple myeloma with bone metastases
2016	America	RCT	Postmenopausal osteoporosis
2018	America	RCT	Multiple myeloma
2018	Greece	RCT	Postmenopausal osteoporosis
2016	America	RCT	Advanced breast with bone metastases Castration-resistant prostate cancer with bone metastases

Skeletal-related events

The SRE rates were reported in four RCTs. The overall SRE rate was 40.5% (37.5% in the Dmab group and 43.5% in the ZA group). Dmab contributed to a lower incidence of SREs (OR = 0.77, 95% CI: 0.70–0.85, p = 0.00001) (Figure 4).

Infection events

Four studies involving 6594 patients were pooled and analyzed. These four trials comparing Dmab with ZA in patients with bone-related disease showed no significant difference between the two drugs in the incidence of infection events (OR = 1.06, 95% CI: 0.93–1.20, p = 0.39) (Figure 5).

Publication bias

Funnel plots for the incidence of adverse events, serious adverse events, infection events and SREs are presented in Figure 6. The funnel plots did not show obvious asymmetry, and only one study (Fizazi, Karim 2011 [7]) evaluating the incidence of serious adverse events lay outside the limits of the 95% CI. Considering that the accuracy of funnel plots might be limited by the small number of studies, we complemented them with Egger's test to statistically examine the publication bias. Egger's test suggested no significant publication bias for the incidence of adverse events (p = 0.310), serious adverse events (p = 0.713), infection events (p = 0.388) or SREs (p = 0.554).

Discussion

We obtained several major findings from the present meta-analysis based on data from 21,042 patients with bone-related diseases. From an efficacy perspective, Dmab resulted in fewer SREs in patients with bone metastases compared with ZA. For medication safety, Dmab significantly reduced the overall rate of adverse events including severe adverse events compared with ZA. Moreover, Dmab did not induce a higher risk of infection.

The benefit of preventing SREs in patients with bone metastases achieved by Dmab was consistently reported across included clinical trials with no interstudy heterogeneity. Previous meta-analyses have also confirmed the advantage of Dmab over ZA in delaying the onset of SREs [21–23]. SREs secondary to bone metastases such as pathological fracture, spinal cord compression, radiation or surgery to bone commonly occur clinically [28], resulting in reduced survival, higher functional independence rates and dramatically lower health-related quality of life [29]. Moreover, SREs impose a considerable financial burden on patients due to subsequent treatments [30, 31]. Although the direct drug cost for Dmab was higher

Table III. Quality assessments of randomized controlled trials enrolled in the meta-analysis

Reference	Score of item I	Score of item II	Score of item III	Score of item IV	Score of item V	Score of item VI	Score of item VII	Score of item VIII	Score of item IX	Score of item X	Score of item XI	Total scores
Athanasios D. Anastasilakis *et al.*	1	1	1	1	1	1	1	1	1	1	1	11
Noopur Raje *et al.*	1	1	1	0.5	1	1	1	1	1	1	1	10.5
Paul D. Miller *et al.*	1	0.5	1	0	1	1	1	1	0.5	1	1	10
Alison T. Stopeck *et al.*	1	1	1	1	1	1	1	1	1	1	1	11
Ingo J. Diel *et al.*	1	1	0.5	0.5	1	0	1	1	0.5	1	1	8.5
Matthew R. Smith *et al.*	1	1	1	0.5	1	1	1	1	0.5	1	1	10
David Henry *et al.*	1	1	1	1	1	1	1	1	1	1	1	11
Giorgio Vittorio Scagliotti *et al.*	1	0.5	1	1	1	1	1	1	1	1	1	10.5
Miguel Martin *et al.*	1	1	1	1	1	1	1	1	1	1	1	11
Saroj Vadhan-Raj *et al.*	1	1	1	1	0.5	1	1	1	1	1	1	10.5
Karim Fizazi *et al.*	1	1	1	0.5	1	1	1	1	1	1	1	10.5
David H. Henry *et al.*	1	1	1	1	1	1	1	1	1	1	1	11
Alison T. Stopeck *et al.*	1	1	1	1	1	1	1	1	1	1	1	11

Study or Subgroup	Denosumab Events	Total	Zoledronic Events	Total	Weight	Odds ratio M-H, Fixed, 95% CI
Alison 2010	977	1020	985	1013	6.8%	0.65 [0.40, 1.05]
Alison 2016	421	465	408	452	6.4%	1.03 [0.66, 1.60]
Athanasios 2019	0	30	18	27	3.1%	0.01 [0.00, 0.15]
David 2011	841	878	842	878	5.8%	0.97 [0.61, 1.55]
David 2013	757	792	751	786	5.5%	1.01 [0.62, 1.63]
Giorgio 2012	393	406	377	395	2.0%	1.44 [0.70, 2.99]
Ingo 2015	1836	1912	1853	1910	12.1%	0.74 [0.52, 1.05]
Karim 2011	341	950	386	951	40.5%	0.82 [0.68, 0.99]
Miller 2016	199	320	199	320	12.3%	1.00 [0.73, 1.30]
Raje 2018	816	850	825	852	5.4%	0.79 [0.47, 1.31]
Total (95% CI)		**7623**		**7584**	**100.0%**	**0.84 [0.75, 0.94]**
Total events	6581		6644			

Heterogeneity: $\chi^2 = 16.46$, $df = 9$ ($p = 0.06$), $I^2 = 45\%$

Test for overall effect: $Z = 2.94$ ($p = 0.003$)

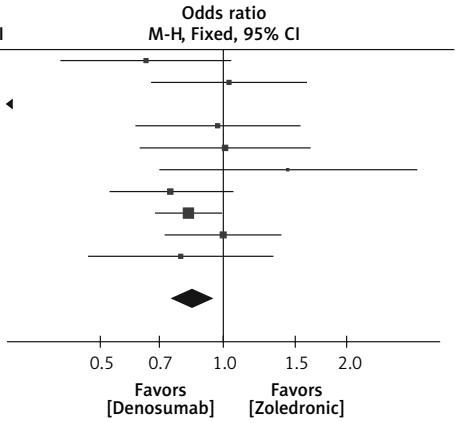

Figure 2. Forest plot for the incidence of adverse events in denosumab compared with zoledronic acid

Study or Subgroup	Denosumab Events	Total	Zoledronic Events	Total	Weight	Odds ratio M-H, Random, 95% CI
Alison 2010	453	1020	471	1013	14.3%	0.92 [0.77, 1.09]
Alison 2016	204	465	196	452	7.4%	1.02 [0.79, 1.33]
David 2011	552	878	581	878	12.0%	0.87 [0.71, 1.05]
David 2013	502	792	534	786	10.9%	0.82 [0.66, 1.01]
Giorgio 2012	268	406	288	395	5.7%	0.72 [0.53, 0.98]
Ingo 2015	1013	1912	1070	1910	22.2%	0.88 [0.78, 1.00]
Karim 2011	594	943	568	945	13.1%	1.13 [0.94, 1.36]
Miller 2016	25	320	29	320	1.8%	0.85 [0.49, 1.49]
Raje 2018	391	850	403	852	12.6%	0.95 [0.78, 1.15]
Total (95% CI)		**7586**		**7551**	**100.0%**	**0.91 [0.85, 0.99]**
Total events	4002		4140			

Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 9.93$, $df = 8$ ($p = 0.27$), $I^2 = 19\%$

Test for overall effect: $Z = 2.30$ ($p = 0.02$)

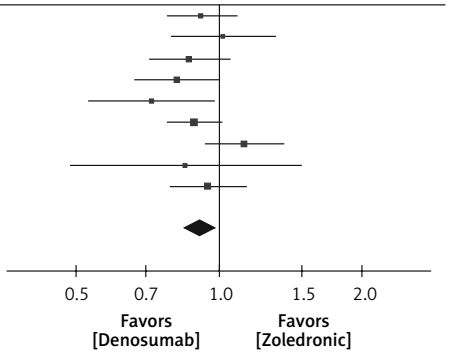

Figure 3. Forest plot for the incidence of serious adverse events in denosumab compared with zoledronic acid

Study or Subgroup	Denosumab Events	Total	Zoledronic Events	Total	Weight	Odds ratio M-H, Fixed, 95% CI
Karim 2011	341	950	386	951	24.7%	0.82 [0.68, 0.99]
Miguel 2012	318	1026	367	1020	25.3%	0.80 [0.66, 0.96]
Smith 2015	494	950	584	951	27.9%	0.68 [0.57, 0.82]
Vadhan 2012	278	886	323	890	22.1%	0.80 [0.66, 0.98]
Total (95% CI)		**3812**		**3812**	**100.0%**	**0.77 [0.70, 0.85]**
Total events	1431		1660			

Heterogeneity: $\chi^2 = 2.51$, $df = 3$ ($p = 0.47$), $I^2 = 0\%$

Test for overall effect: $Z = 5.43$ ($p < 0.00001$)

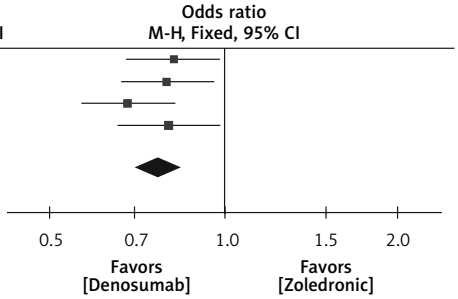

Figure 4. Forest plot for the incidence of SREs in denosumab compared with zoledronic acid

Study or Subgroup	Denosumab Events	Total	Zoledronic Events	Total	Weight	Odds ratio M-H, Random, 95% CI
Alison 2010	473	1020	494	1013	32.8%	0.91 [0.76, 1.08]
Alison 2016	193	465	168	452	10.4%	1.20 [0.92, 1.56]
David 2011	128	878	118	878	17.9%	1.10 [0.84, 1.44]
Karim 2011	402	943	375	945	30.8%	1.13 [0.94, 1.36]
Total (95% CI)		**3306**		**3288**	**100.0%**	**1.06 [0.93, 1.20]**
Total events	1196		1155			

Heterogeneity: $\tau^2 = 0.01$, $\chi^2 = 4.34$, $df = 3$ ($p = 0.23$), $I^2 = 31\%$

Test for overall effect: $Z = 0.85$ ($p = 0.39$)

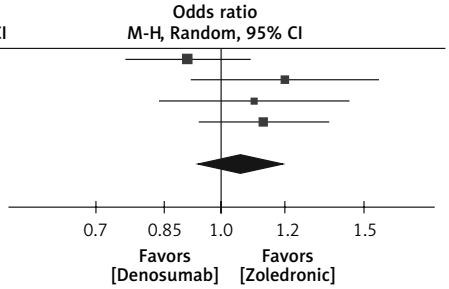

Figure 5. Forest plot for the incidence of infection events in denosumab compared with zoledronic acid

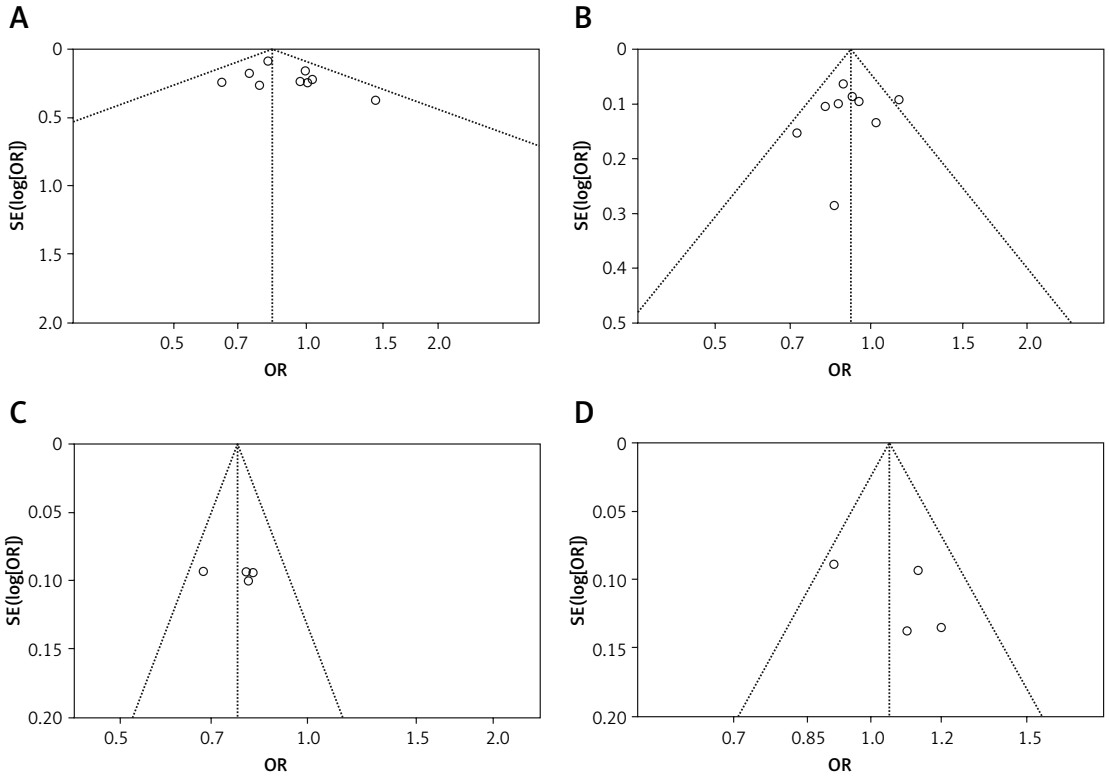

Figure 6. Funnel plots for the incidence of: **A** – adverse events, **B** – serious adverse events, **C** – infection events and **D** – skeletal-related events

than ZA, it can be remarkably offset by reduced costs contributed by preventing or delaying the onset of SREs [19, 20]. Therefore, compared with ZA, Dmab can alleviate both the health and economic burden for patients.

The comparison of the overall adverse events rate between Dmab and ZA has been little evaluated in previous meta-analyses. After processing data from ten RCTs which enrolled a total of 15,207 patients, our analyses indicated that Dmab was superior to ZA in reducing the overall rate of adverse events. Of the ten studies, three included patients with multiple myeloma [8, 10, 32] and two included patients with postmenopausal osteoporosis [5, 18], which relatively well represented the spectrum of indications of antiresorptive regents. Of note, no adverse events were recorded in the Dmab group in one study based on patients with postmenopausal osteoporosis [5], which was also the major source of heterogeneity. One potential explanation was that all patients underwent previous treatment of Dmab with a mean duration of 2.2 years before the start of the trial and thus well tolerated a second course of Dmab treatment. After excluding this study for sensitivity analysis, the result remained significant with a remarkable decrease in heterogeneity ($p = 0.020$, $I^2 = 0$). Moreover, Dmab was also associated with fewer serious adverse events after evaluating data from nine clinical trials. A previous meta-analysis based on patients with bone metastases demonstrated that Dmab administration was associated with lower risk of serious adverse events including hypocalcemia, new primary malignancy and particularly renal toxicity [16], which together with the results of our meta-analysis confirmed that Dmab had advantages in reducing the occurrence of serious adverse events over ZA.

The RANKL pathway is expressed in activated lymphocytes and is involved in the formation of lymphoid nodes and the thymic microenvironment [33, 34], and its inhibition by Dmab was found to be correlated with a higher risk of infection. As shown by the results of our analysis, Dmab did not significantly increase the incidence of infection events compared with ZA. However, according to the pooled estimate of four included clinical trials, the overall rate of infection after infusion of Dmab was 36.2%. Additionally, serious and opportunistic infections have been observed, though rarely, in patients treated with Dmab [35, 36]. Therefore, Dmab-induced infection still merits consideration before the initiation of therapy.

The present meta-analysis provided an assessment of current evidence regarding the efficacy and safety of Dmab versus ZA based on 13 high-quality RCTs which covered several bone-related diseases. To our current knowledge, compared with previous studies regarding the related topic, this meta-analysis contains the largest

number of RCTs and covers the widest range of bone-related diseases, contributing to a reliable result and a more extensive application of analysis results. Despite these strengths, our study has several limitations. Even though the studies included in our meta-analysis were not confined to bone metastases, the number of studies evaluating non-cancer diseases such as postmenopausal osteoporosis was too small to conduct a reliable and robust subgroup analysis, which may limit the generalization of our results. For osteoporosis, the results must be interpreted with caution, and a subgroup analysis is warranted with more articles published. Also, some included studies were sponsored by pharmaceutical companies, and as such they were not free of potential pharmaceutical company bias.

Conclusions

Based on 13 high-quality randomized clinical trials, our results demonstrated that Dmab was superior to ZA in reducing the overall rate of adverse events as well as serious adverse events, and in reducing the onset of SREs. The treatment of denosumab was not correlated with a higher risk of infection as previously found. Considering the superiority of denosumab in safety outcomes, denosumab will be regarded as an optimal intervention for bone-related diseases. However, for bone-related diseases other than bone metastases, the superior safety of denosumab should be generalized with caution and further analyses are still warranted.

Conflict of interest

The authors declare no conflict of interest.

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