Journal of Reviews in Medical Sciences. 2021; 1(2): e97
DOI: 10.22034/jrms.2021.366825.1010

Meta-analysis

Effects of Tanezumab on Osteoarthritis of the Knee: A Systematic Review and Meta-Analysis

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Received: February 2021; Accepted: March 2021; Published online: April 2021

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ABSTRACT

Background: Tanezumab is known as a new medical treatment for patients with osteoarthritis (OA) of the knee. We performed this meta-analysis to investigate the efficacy and safety of Tanezumab for treatment of patients with knee OA.

Methods: We systematically searched randomized controlled trials from MEDLINE, Scopus, EMBASE, EBSCO, and the Cochrane Central Register of Controlled Trials (CENTRAL). The selected primary outcomes for this study were mean change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, the WOMAC physical function and patient's global assessment (PGA). Outcomes were reported using the standard mean difference (SMD) or odds ratio (OR) with 95% confidence interval (CI). We evaluated the pooled data using a random and fixed effects models.

Results: Of the studies that were found during systematic search, five studies were eligible and were included in this meta-analysis. Compared with the placebo groups, tanezumab showed a significant more reduction in mean of the WOMAC pain (SMD = -0.92, 95% CI -1.47 to -0.37, P=0.001), the WOMAC physical function (SMD = -0.59, 95% CI -0.79 to -0.39, P<0.01), and PGA (SMD = -0.36, 95% CI -0.45 to -0.27, P<0.01). There was no significant difference in serious adverse events (OR = 1.38, 95% CI 0.59 to 3.21, P = 0.48) between the tanezumab and placebo groups. Placebo significantly decreased discontinuations due to adverse events (OR = 0.37, 95% CI 0.21 to 0.64, P = 0.001), abnormal peripheral sensations (OR = 0.32, 95% CI 0.21 to 0.50, P<0.01), and peripheral neuropathy (OR = 0.25, 95% CI 0.13 to 0.48, P<0.01).

Conclusion: This meta-analysis showed that Tanezumab can decrease pain and improve function for patients with OA of the knee. However, due to the limited number of studies, this conclusion should be interpreted cautiously and further clinical randomized controlled trials will be required to approve the efficacy and safety of tanezumab for OA of the knee.

Keywords: knee, Osteoarthritis, Tanezumab, Systematic review, Meta-analysis.

Introduction

Osteoarthritis (OA) of the knee is the most common type of OA (1), which leads to pain, limits activity, and is associated to a decreased quality of life (2). It was reported that the worldwide prevalence of OA of the knee was 3.8% in 2010 (3), and this rate will more increase as the proportion of elderly population rises. Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are suggested as the first line treatments for alleviation of the pain of knee OA (4). Although patients show a higher analgesic effect from them over other analgesics, these treatments may have a suboptimal therapeutic effect on some patients (5, 6), and some patients show some complications such as hepatotoxicity, gastrointestinal toxicity and cardiorenal effects (7). Nerve growth factor (NGF), which has a pivotal role in pain reduction, is a new therapeutic target for pain treatment (8). All experimental studies and clinical trials reveal that antagonism of NGF may be a possible therapeutic target for chronic pain (9). Tanezumab, a humanized monoclonal antibody against NGF, inhibits activation of TrkA receptors on nociceptive neurons (10). Although previous randomized controlled trials have suggested that tanezumab significantly reduces pain and increases physical function in patients with knee OA, the relatively small sample size of the studies have made their conclusions inconclusive (11). In a recent meta-analysis that compared anti-NGF antibody treatment with placebo in patients with OA of the hip or the knee, the authors reported that Tanezumab can be efficacious for improvement of symptomatic OA (12). Because that study assessed the efficacy and complications of tanezumab for patients with OA of the hip or the knee, we cannot indicate whether tanezumab have a established effect on OA of the knee. Based on the findings of recent clinical studies with tanezumab, we aimed to pool the findings in a meta-analysis. Therefore, in this meta-analysis, we evaluated efficacy and side effects of tanezumab in patients with knee osteoarthritis.

Methods

Search Strategy and Study Selection

We performed this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta- Analysis (PRISMA) guidelines throughout the study (13). We performed a systematic search to find randomized controlled trials that assessed the efficacy of Tanezumab for the treatment of knee OA from MEDLINE, Scopus, EMBASE, EBSCO, and the Cochrane Central Register of Controlled Trials (CENTRAL). The final literature search of the study was up to September 1, 2020. Terms for systematic search were included osteoarthritis, knee, and tanezumab. Boolean operators “AND” and “OR” were used to combine the above-mentioned terms. There were no restriction regarding publication date and we included only English-language studies. We also manually assessed reference lists from the included studies and relevant review studies for possible relevant studies. Two authors independently evaluated the titles and abstracts of papers identified by the retrieval. Finally, the full text of the remaining studies were evaluated according to the eligibility criteria. Disagreement between two authors was resolved by referring to a third reviewer.

Eligibility Criteria

We included only studies enrolling adult patients with a confirmed diagnosis of knee osteoarthritis according to the American College of Rheumatology criteria and grade 2 or higher based on the Kellgren-Lawrence grading system. The treatment in the intervention group was an intravenous administration of tanezumab at any dose and any phase. Studies with patients receiving NSAIDs or other analgesics, except tanezumab, were excluded from the meta-analysis. The treatment in the control group was a placebo. Mean change in the WOMAC pain, the WOMAC physical function and PGA, discontinuations due to adverse events, incidence of serious adverse events, abnormal peripheral sensations, and peripheral neuropathy were the obtained variables as the outcomes. Only randomized controlled trials were assessed as eligible types of the study in our meta-analysis.

Data Extraction

Two authors independently collected some necessary data. Information regarding the author, publication date, characteristics of subjects, intervention and comparisons, duration of follow-up, sample size, and outcomes were extracted. Any inconsistency was settled by a third reviewer to reach a consensus. The primary outcome variables of interest were mean change in the WOMAC pain, the WOMAC physical function and PGA. The secondary outcome variables were included discontinuations due to adverse events, incidence of

serious adverse events, abnormal peripheral sensations, and peripheral neuropathy.

Data Synthesis

For mean change in the WOMAC pain, the WOMAC physical function and PGA, we used the standard mean difference (SMD) and 95% confidence interval (CI). For dichotomous outcomes, we used the relative risk (RR) and 95% CI.

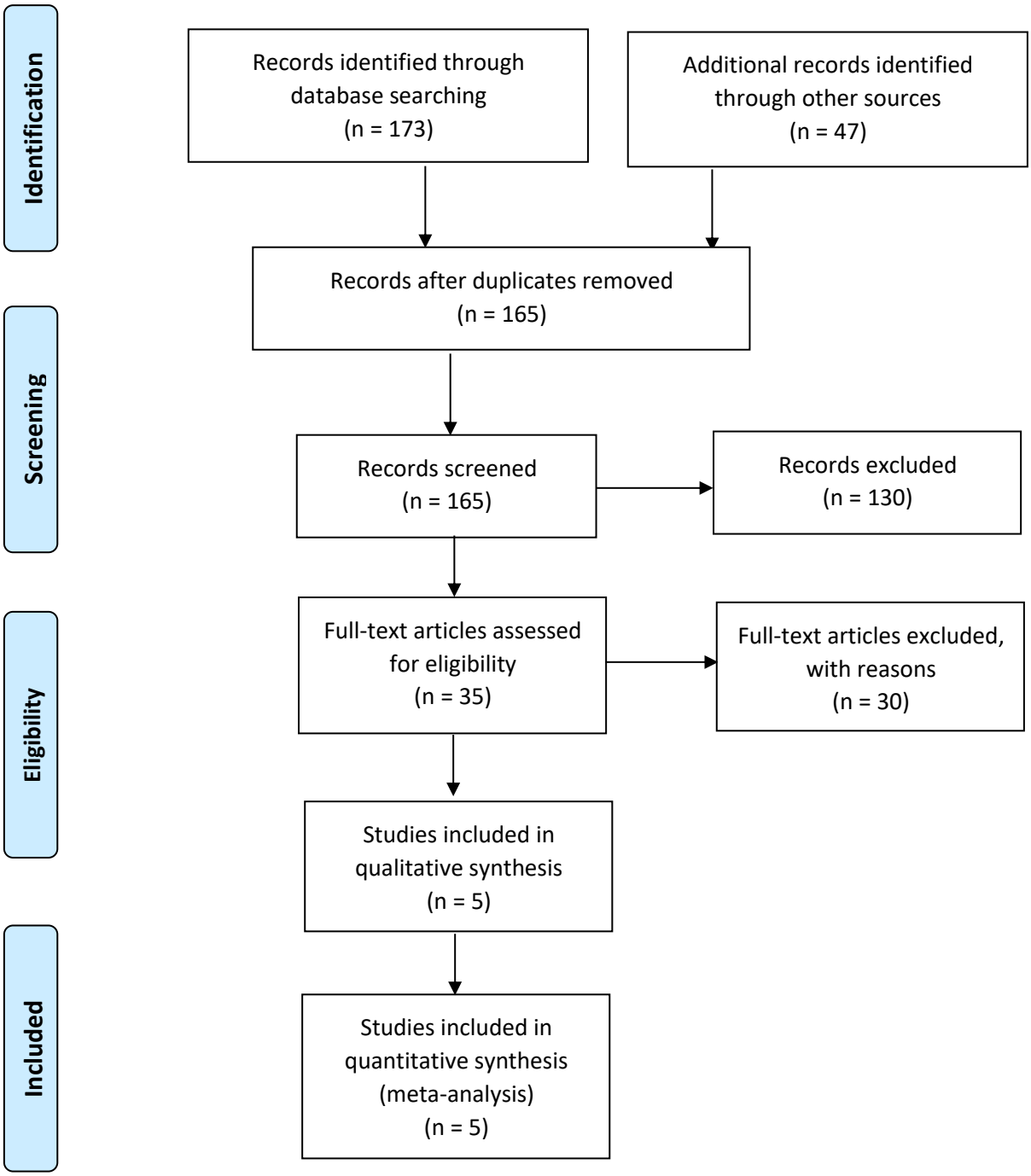

Figure 1. PRISMA flowchart of the literature search and selection of studies that reported complication rate after ultrasound-guided core needle biopsy of thyroid nodules.

A random-effects model was utilized to estimate the pooled outcomes according to the results of assessment of heterogeneity.

We assessed heterogeneity using the I^2 statistic, which showed the amount of heterogeneity among included clinical trials. Heterogeneity was

considered to be statistically significant if the I^2 value was greater than 50% or P-value was less than 0.05. For changes in the WOMAC pain, the WOMAC physical function, and PGA, subgroup analyses were carried out in accordance with the administration frequency and the phase of the trial. Moreover, we used sensitivity analyses to assess the robustness of the study results by using a fixed-effects model and removing trials one by one. To find the publication bias, we used Egger's test and funnel plots. A P value less than 0.05 was considered as statistically significant. All statistical analyses were performed using Comprehensive Meta-Analysis software (CMA, ver. 2).

Results

Study Search

PRISMA flowchart of the systematic search and selection of studies are summarized in figure 1. Initially, we identified 220 relevant studies, of which 55 were excluded because of duplicates and 130 did not meet the eligibility criteria at the title and abstract level.

Table 1. Characteristics of the included studies in the meta-analysis.

Authors	Country	Phase of Trial	Intervention	Patients (Number)	Age	Male (%)	Follow up
Lane 2010	USA	II	Placebo	74	58.1	43	16 W
			TNZ 10 µg/kg	74	58.3	34	16 W
			TNZ 25 µg/kg	74	59.9	32	16 W
			TNZ 50 µg/kg	74	60.4	50	16 W
			TNZ 100 µg/kg	74	57.1	41	16 W
			TNZ 200 µg/kg	74	58.4	46	16 W
Nagashima 2011	Japan	II	Placebo	16	59.4	31.3	13 W
			TNZ 10 µg/kg	15	59.3	33.3	13 W
			TNZ 25 µg/kg	15	57.3	46.7	13 W
			TNZ 50 µg/kg	15	60.7	26.7	13 W
			TNZ 100 µg/kg	16	58.1	25	13 W
			TNZ 200 µg/kg	6	60	16.7	13 W
Brown 2012	USA	III	Placebo	172	62.2	30.8	32 W
			TNZ 2/5 mg/day	172	60.8	45.3	32 W
			TNZ 5 mg/day	172	62.1	41.3	32 W
			TNZ 10 mg/day	174	61.4	39.1	32 W
Ekman 2014	USA	III	Placebo	208	60.9	42.3	24 W
			TNZ 5 mg/day	206	61.1	40.8	24 W
			TNZ 10 mg/day	208	61.1	38.5	24 W
Berenbaum 2020	Europe	III	Placebo	282	64.2	30.5	24 W
			TNZ 2/5 mg/day	283	65.2	30	24 W
			TNZ 5 mg/day	284	65.2	32	24 W

After a review of the full text in the remaining 35 studies, six study was excluded for not being a randomized controlled trial, five for being a letter, and 19 for being conference abstracts. Finally, we

included five eligible records in the quantitative analysis.

Study Characteristics

The baseline characteristics of the included randomized controlled trials were outlined in Table 1. There were 5 studies with 17 pair-wise comparison groups included in our meta-analysis. All the included studies were sponsored by pharmaceutical companies. Naproxen was considered as intervention for control group in one study (14). However, as naproxen did not conform to our inclusion criteria, we removed the participants treated with naproxen. Two studies (11, 15) were phase II trials, and the other two (14, 16) were phase III trials.

Three studies were carried out in America, one study was performed in Europe, and the other one was conducted in Japan. All of the studies were published in English, between 2011 and 2020. Fig 2 shows the details of the risk of bias evaluation for all of the studies. Egger's test showed no significant publication bias in terms of studies comparing the mean change in WOMAC Pain (P=0.68).

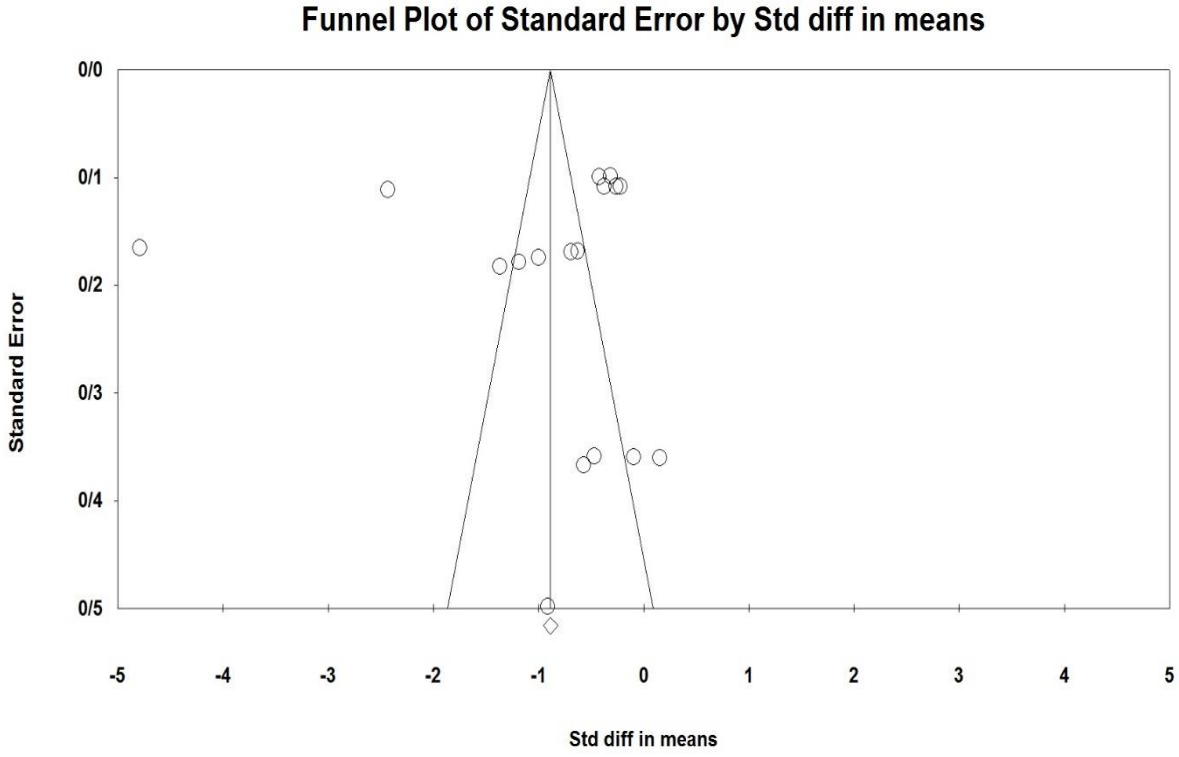

Figure 2. Funnel plot of results of studies comparing the mean change in WOMAC Pain.

Outcomes

Five studies with 17 pair-wise comparison groups, including 2682 patients with knee OA, assessed the effect of tanezumab on the mean included in this meta-analysis to estimate the effect of tanezumab on the mean change in the WOMAC pain. Compared with the placebo groups, tanezumab showed a significant more reduction in mean of the WOMAC pain (SMD = -0.92, 95% CI -1.47 to -0.37, P=0.001), the WOMAC physical function (SMD = -0.59, 95% CI -0.79 to -0.39, P<0.01), and PGA (SMD = -0.36, 95% CI -0.45 to -0.27, P<0.01). (Fig 3b). There was no significant difference in serious adverse events (OR = 1.38, 95% CI 0.59 to 3.21, P = 0.48) between the tanezumab and placebo groups. Placebo significantly decreased discontinuations due to adverse events (OR = 0.37, 95% CI 0.21 to 0.64, P = 0.001), abnormal peripheral sensations (OR = 0.32, 95% CI 0.21 to 0.50, P<0.01), and peripheral neuropathy (OR = 0.25, 95% CI 0.13 to 0.48, P<0.01) (Fig 4).

Discussion

In the current meta-analysis, we investigated the efficacy and side effects of tanezumab for patients with OA of the knee. On the basis of the pooled estimates, tanezumab, compared with the placebo, was correlated with a significant reduction in the mean change in the WOMAC pain, the WOMAC physical function and PGA. The use of tanezumab

was not correlated with a significantly increased risk of serious adverse events, but it increased the odds of discontinuations due to adverse events, abnormal peripheral sensations, and peripheral neuropathy.

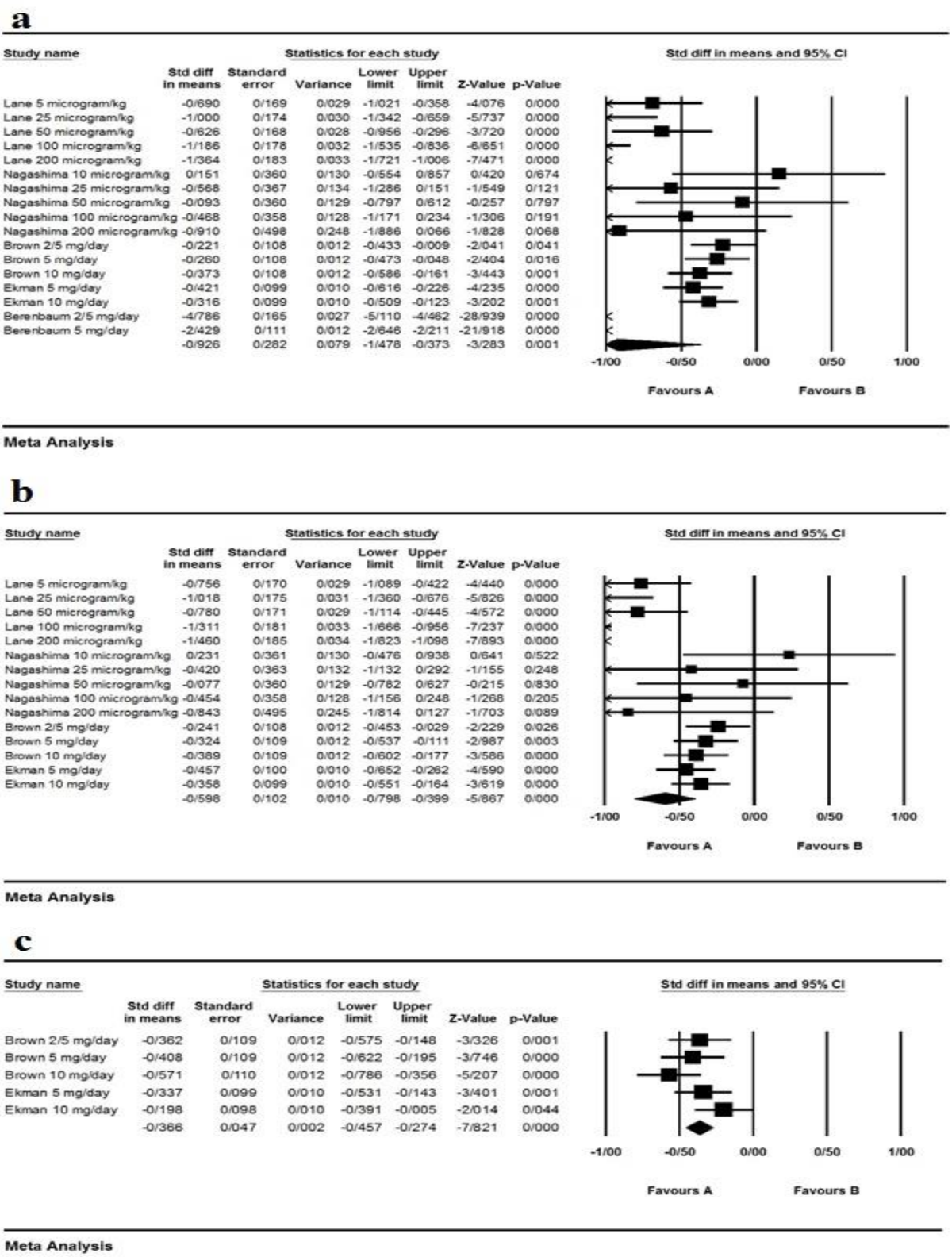

Figure 3. Forest plots of the included studies comparing the mean change in WOMAC Pain (a), WOMAC Physical Function (b), and PGA (c) in patients who received tanezumab and placebo.

The current meta-analysis showed that tanezumab had a beneficial effect on the WOMAC pain, the WOMAC physical function and PGA. In a recent meta-analysis of 13 studies comparing anti-NGF antibody treatment with a placebo in patients with OA of the hip or the knee, the authors (12) showed that tanezumab appeared to be efficacious to improve the WOMAC pain, the WOMAC physical function and PGA.

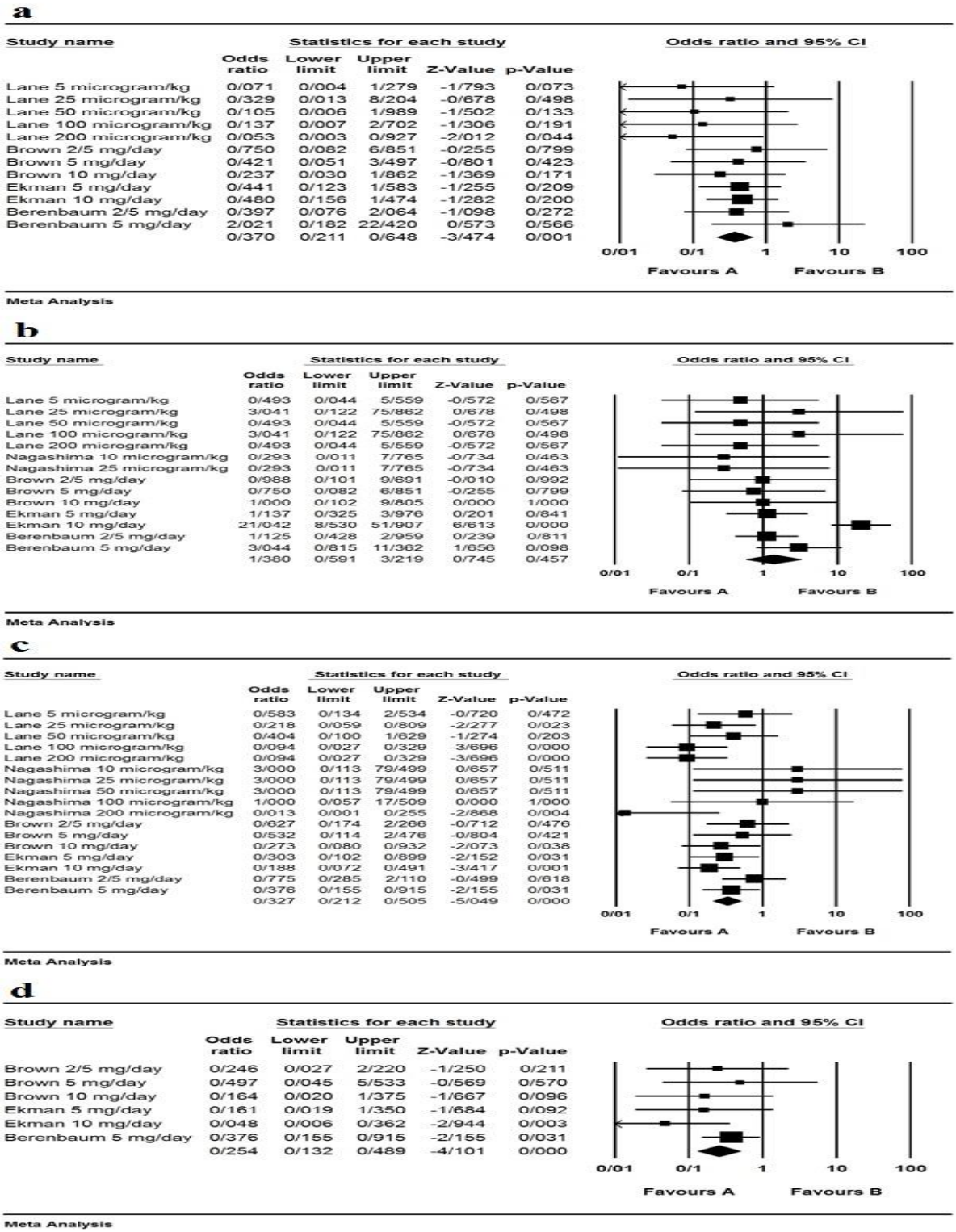

Figure 4. Forest plots of the included studies comparing discontinuations due to adverse events (a), serious adverse events (b), abnormal peripheral sensations (c), and peripheral neuropathy (d) in patients who received tanezumab and placebo.

Although that finding was in line with our research, that study was aimed to assess the efficacy and safety of tanezumab for patients with OA of the hip or the knee. Therefore, we could not conclude that tanezumab has an approved significant influences on the WOMAC pain, the WOMAC physical function and PGA among only patients with knee OA. Thus, further large scale trials are needed to approve the effect of tanezumab on patients with knee OA. The effect of tanezumab on the WOMAC pain, the WOMAC physical function and PGA was comparable to the effects of the presently recommended NSAIDs or paracetamol (17). Based on a network meta-analysis (18) of 137 studies in 33,243 adults with knee OA, ibuprofen was correlated with a significant improvement in pain reduction and increase of physical function at 3 months; and diclofenac was correlated with a significant pain reduction and improvement in physical function at 3 months. In a meta-analysis comparing the relative efficacies of NSAID therapies with that of a placebo, all NSAIDs were reported to reduce pain (19). Although both NSAIDs and tanezumab decrease pain, tanezumab is different from NSAIDs with respect to its effects on pain reduction. This may be due to that tanezumab specifically blocks the activation of TrkA by NGF, rather than inhibiting the cyclooxygenase pathways (10, 20). Both experimental and clinical investigations have indicated that NGF plays a significant role in the generation and maintenance of pain (10, 21). In human studies, there were increased NGF levels found in the synovial fluid of subjects with inflammatory, rheumatoid arthritis or osteoarthritis (22). In addition, blockage of NGF action significantly reduced hyperalgesia and pain perception in animal studies with acute local inflammation, chronic inflammatory arthritis or osteoarthritis (23). Regarding the safety of tanezumab, the current meta-analysis revealed a significantly increased risk of discontinuations due to adverse events, abnormal peripheral sensations, and peripheral neuropathy. Some discontinuations were seemed not to be associated to the study drug (16). No significant differences in serious adverse events were detected between tanezumab and a placebo. Serious adverse events were shown in the studies included appendicitis, bacterial arthritis, cellulitis, spinal stenosis, breast cancer, syncope, inguinal hernia, atrioventricular block, and contusion, although some of them were seemed to be irrelevant to tanezumab. There are some pivotal findings of the present meta-analysis. Our meta-analysis was carried out and analyzed in conformity with the best practice methods suggested by the Cochrane Collaboration (24). During systematic search, including MEDLINE, EMBASE, EBSCO, Scopus, and CENTRAL, was carried out without language restriction. We used strict and broad inclusion criteria to find all of the eligible randomized controlled trials in this field. Two reviewers independently assessed the risk of bias of the individual studies and evaluated the quality of the evidence according to the GRADE approach.

Our meta-analysis also has some possible limitations that should be considered when reporting the benefits. First, our analysis included only four randomized controlled trials, but one of them had a modest sample size (n<100). Compared to large sample size studies, small sample size studies are inclined regarding overestimation of the effect of intervention (25), which limits the power of inference. Second, we could not assess the potential risk of publication bias due to the small number of included studies, although our literature search is supposed to be exhaustive. Meanwhile, the limited number of studies may also have affected our conclusions. Moreover, the follow-up of patients in the included studies was limited. Patients were followed up ranging from 13 to 32 weeks after the initial dose of tanezumab. This may cause an underestimation of side effects. In addition, all of the included studies were sponsored by pharmaceutical companies. This may also have an effect on the validity of our conclusions.

Conclusions

In conclusion, the present meta-analysis showed that tanezumab can reduce pain and increase function. Moreover, tanezumab was not correlated with a significantly increased incidence of serious adverse events but was correlated with significant increases in discontinuations due to adverse events, abnormal peripheral sensations and peripheral neuropathy. Due to the limited number of studies, the conclusion should be applied cautiously, and further clinical randomized controlled trials are required to approve the efficacy and safety of tanezumab for OA of the knee.

Declarations

Acknowledgement

The authors thank all those who contributed to this study.

Author Contribution

Reza Noktehsanj: Study design, data collection, and writing draft of study.

Sayed-Mohammad-Amin Nourian: Study design, data collection, and writing draft of study.

Farzad Amouzadeh-Omrani: Study design, data collection, and writing draft of study.

Keyvan Amini: Study design, data collection, and writing draft of study.

Funding/Support

No funding was provided for this study.

Conflict of interest

There is no conflict of interest.

Data Availability

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

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