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Meta-analysis

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

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ABSTRACT

Background: Tanezumab is a new therapeutic intervention for patients with osteoarthritis (OA) of the knee. We performed the present meta-analysis to appraise the efficacy and safety of Tanezumab for patients with knee OA.

Methods: We systematically searched randomized controlled trials from PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL). The primary outcomes 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 as the standard mean difference (SMD) or odds ratio (OR) with 95% confidence interval (CI). We assessed the pooled data using a random and fixed effects models.

Results: Of the identified studies, five were eligible and were included in this meta-analysis. Compared with the placebo groups, tanezumab yielded 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: Tanezumab can alleviate pain and improve function for patients with OA of the knee. However, considering the limited number of studies, this conclusion should be interpreted cautiously and more clinical randomized controlled trials are needed to verify 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 location of OA (1), which causes pain, limits activity, and leads to a decreased quality of life (2). It was estimated that the global prevalence of OA of the knee was 3.8% in 2010 (3), and this number will further increase as the elderly population rises. Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as the first line treatment drugs for painful knee OA (4). Although patients experience a greater analgesic effect from them over other analgesics, these medications may have a suboptimal therapeutic effect on some patients (5, 6), and some patients experience the risk of hepatotoxicity, gastrointestinal toxicity and cardiorenal side effects (7). Nerve growth factor (NGF), which plays a crucial role in pain modulation, is a new therapeutic target for pain therapy (8). All experimental and clinical trials indicate that antagonism of NGF may be a feasible therapeutic option for chronic pain (9). Tanezumab, a humanized monoclonal antibody, blocks NGF from activating TrkA receptors on nociceptive neurons (10). Although recent randomized controlled trials have suggested that tanezumab significantly alleviates pain and improves physical function in patients with OA of the knee, the relatively small number of participants have made their conclusions inconclusive (11). In a previous meta-analysis comparing an anti-NGF antibody treatment with a placebo in patients with OA of the hip or the knee, Schnitzer and colleagues found that Tanezumab appeared to be efficacious in improving symptomatic OA (12). Because that study investigated the efficacy and safety of tanezumab for patients with OA of the hip or the knee, we cannot determine whether tanezumab is certain to have a significant influence on OA of the knee. Based on the current clinical studies with tanezumab, we tried to pool the results in a meta-analysis. Therefore, in this meta-analysis, we aimed to assess efficacy and complications of tanezumab in patients with knee osteoarthritis.

Materials and Methods

Search Strategy and Study Selection

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta- Analysis (PRISMA) guidelines throughout the study (13). We systematically searched randomized controlled trials that investigated the use of Tanezumab for the treatment of knee OA from PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL). The most recent literature search was up to July 25, 2015. Search terms included tanezumab and knee osteoarthritis. Boolean operators “AND” and “OR” were utilized to couple these terms. The details of the search strategy are displayed in S1 Table. There were no restrictions regarding language and publication date. We also manually retrieved reference lists from the identified studies and relevant review studies for additional relevant studies. Two investigators independently assessed the titles and abstracts of studies identified by the retrieval. Then, the full text of the remaining studies were reviewed according to the eligibility criteria. Disagreement was settled by referring to a third reviewer.

Eligibility Criteria

Only studies enrolling adult participants with a 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 intervention in the experimental group was an intravenous administration of tanezumab at any dose and any phase. Studies with participants receiving NSAIDs or other analgesics, except tanezumab, were excluded. The intervention 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 collected as the outcomes. Only randomized controlled trials were regarded as eligible in our study.

Data Extraction

Two researchers independently abstracted some necessary information. Information concerning the author, publication year, participant characteristics, intervention and comparison, duration of follow-up, sample size, and outcome were recorded. Any discrepancy was resolved by a joint review of the article to reach a consensus. The primary outcome measures of interest were mean change in the WOMAC pain, the WOMAC physical function and PGA (using any score or scale). The secondary outcome measures comprised 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 calculated the standard mean difference (SMD) and 95% confidence interval (CI). For dichotomous outcomes, we calculated the relative risk (RR) and 95% CI. A random-effects model was applied to estimate the pooled outcomes without regarding heterogeneity.

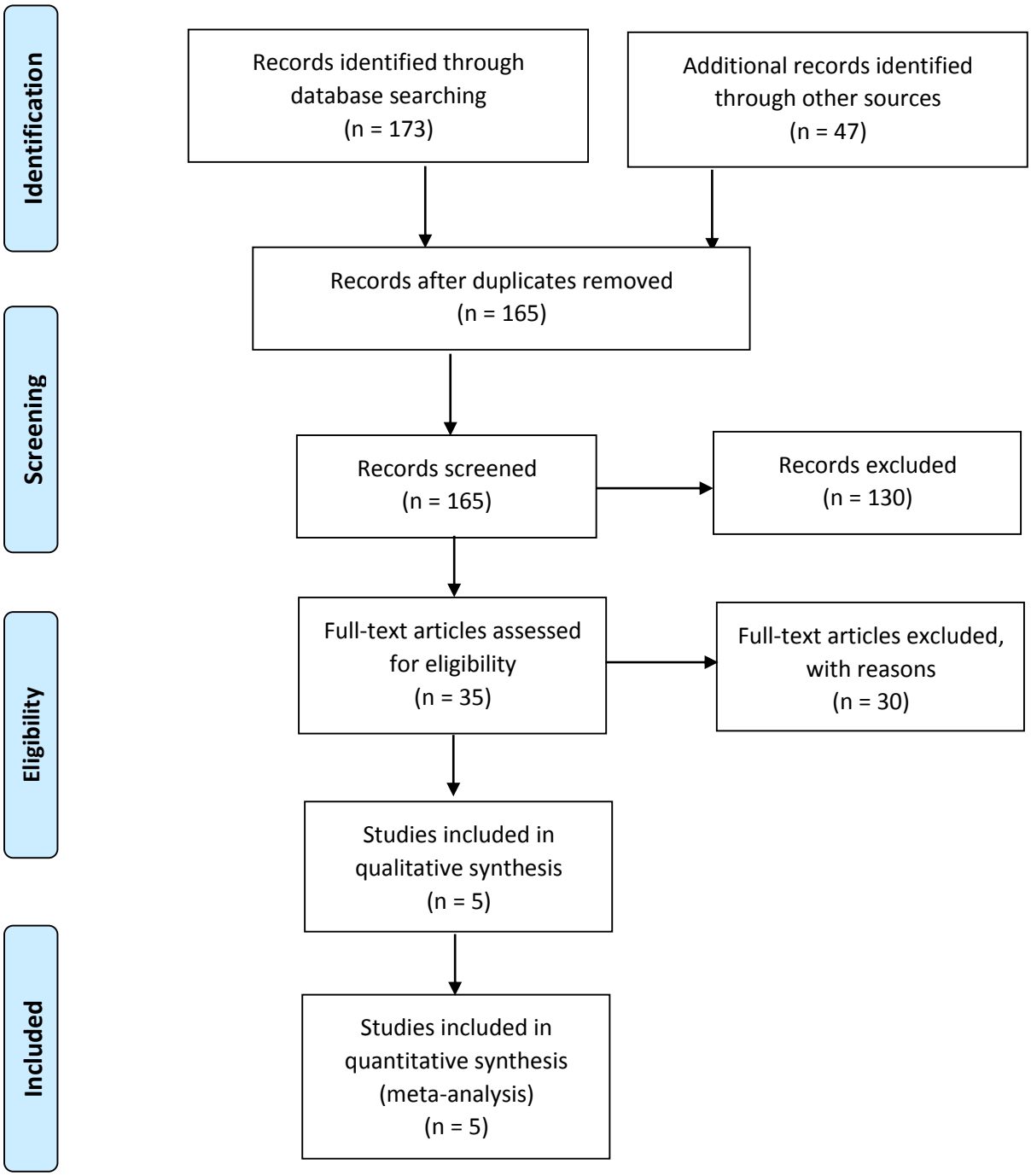

Figure 1. PRISMA flowchart of the literature search and selection of studies that reported complication rate after ultrasound-guided core needle biopsy of thyroid nodules.

We evaluated heterogeneity using the I2 statistic, which mirrored the amount of heterogeneity across trials. Heterogeneity was considered to be statistically significant if the I2 value was greater than 50%. For changes in the WOMAC pain, the WOMAC physical function, and PGA, subgroup analyses were performed in accordance with the administration frequency (twice versus three times) and the phase of the trial (phase II versus phase III). Furthermore, we implemented sensitivity analyses to verify the robustness of the study results by using a fixed-effects model and removing trials one by one. To detect the publication bias, we utilized Egger's linear regression test and funnel plots for primary outcomes if the number of the studies was larger than ten. A P value less than 0.05 was regarded as statistically significant. All statistical analyses were conducted using Comprehensive Meta-Analysis software (CMA, ver. 3).

Results

Study Search

Flowchart of the literature search and selection of studies are shown 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, one 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 studies were sponsored by pharmaceutical companies. Naproxen acted as a control in one study (14). However, as naproxen did not conform to our inclusion criteria, we discarded 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 performed in America, one study was carried out in Europe, and the other one was conducted in Japan. All of the articles were published in English, between 2011 and 2020. Fig 2 outlines the details of the risk of bias assessment for all of the studies. Egger's test revealed no significant publication bias in terms of studies comparing the mean change in WOMAC Pain (P=0.68).

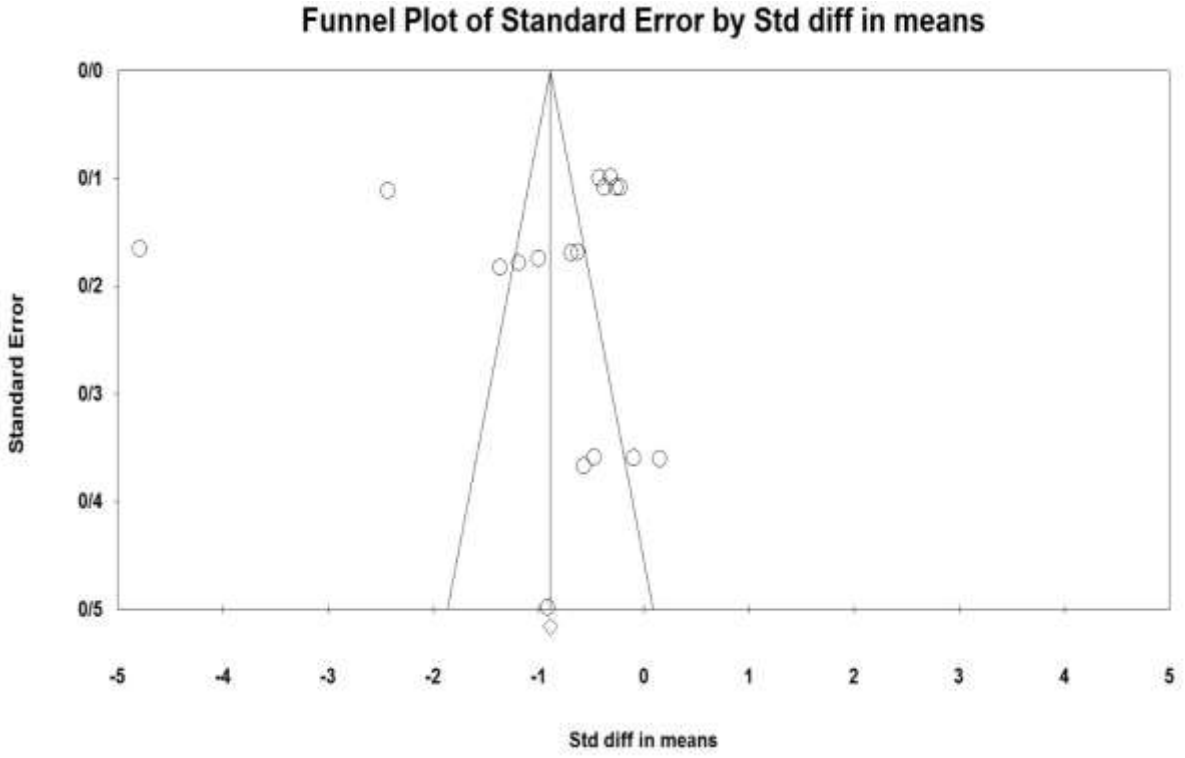

Figure 2. Funnel plot of results of studies comparing the mean change in WOMAC Pain.

Outcomes

Five studies with 17 pair-wise comparison groups, including 2682 patients with knee OA, tested 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 yielded 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 evaluated the efficacy and safety of tanezumab for patients with OA of the knee. On the basis of the pooled estimates, tanezumab, compared with the placebo, was

associated with a significant reduction in the mean change in the WOMAC pain, the WOMAC physical function and PGA. The use of tanezumab was not associated 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.

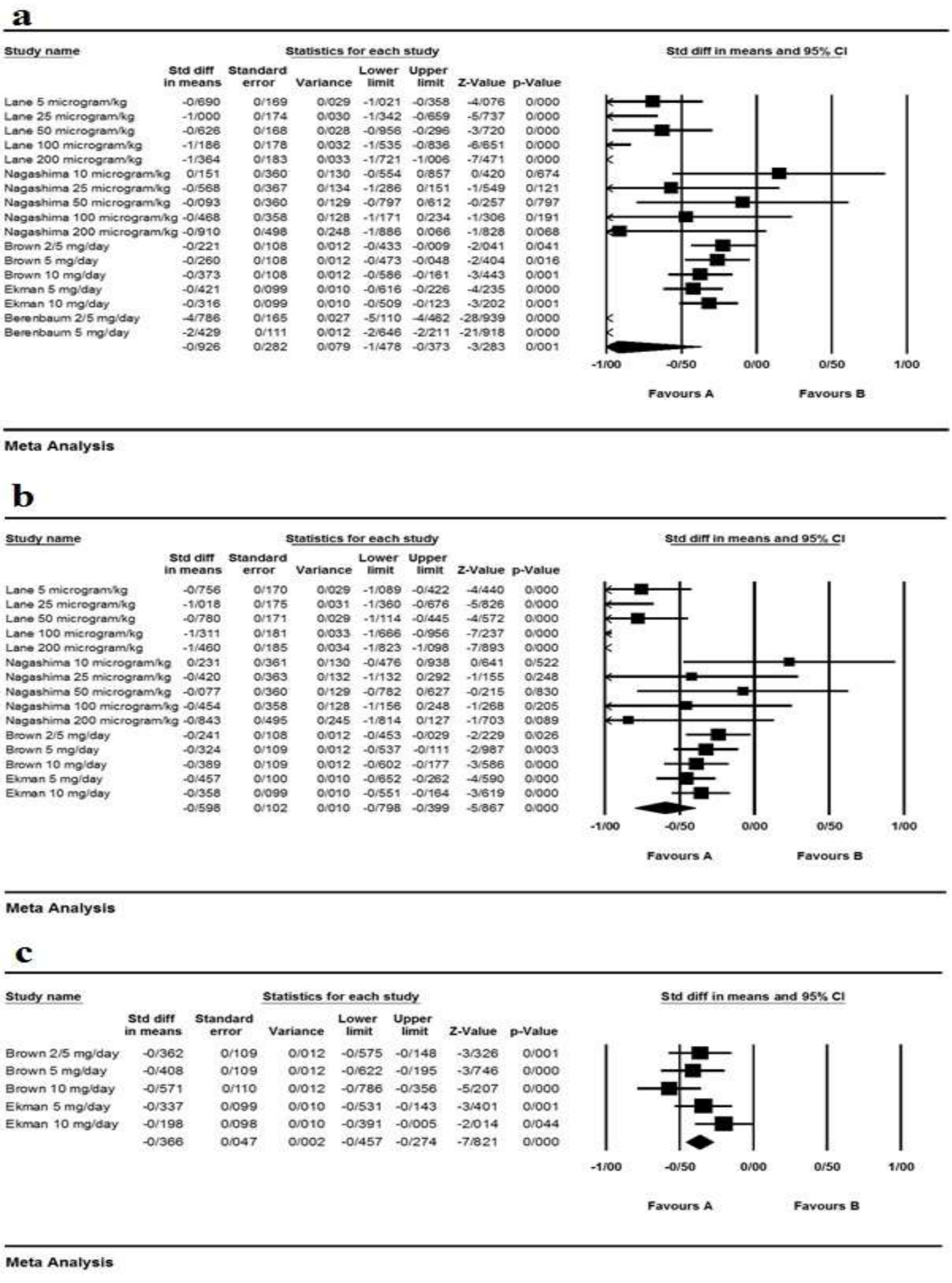

Figure 3. Forest plots of the included studies comparing the mean change in WOMAC Pain (a), WOMAC Physical Function (b), and PGA (c) in patients who received tanezumab and placebo.

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

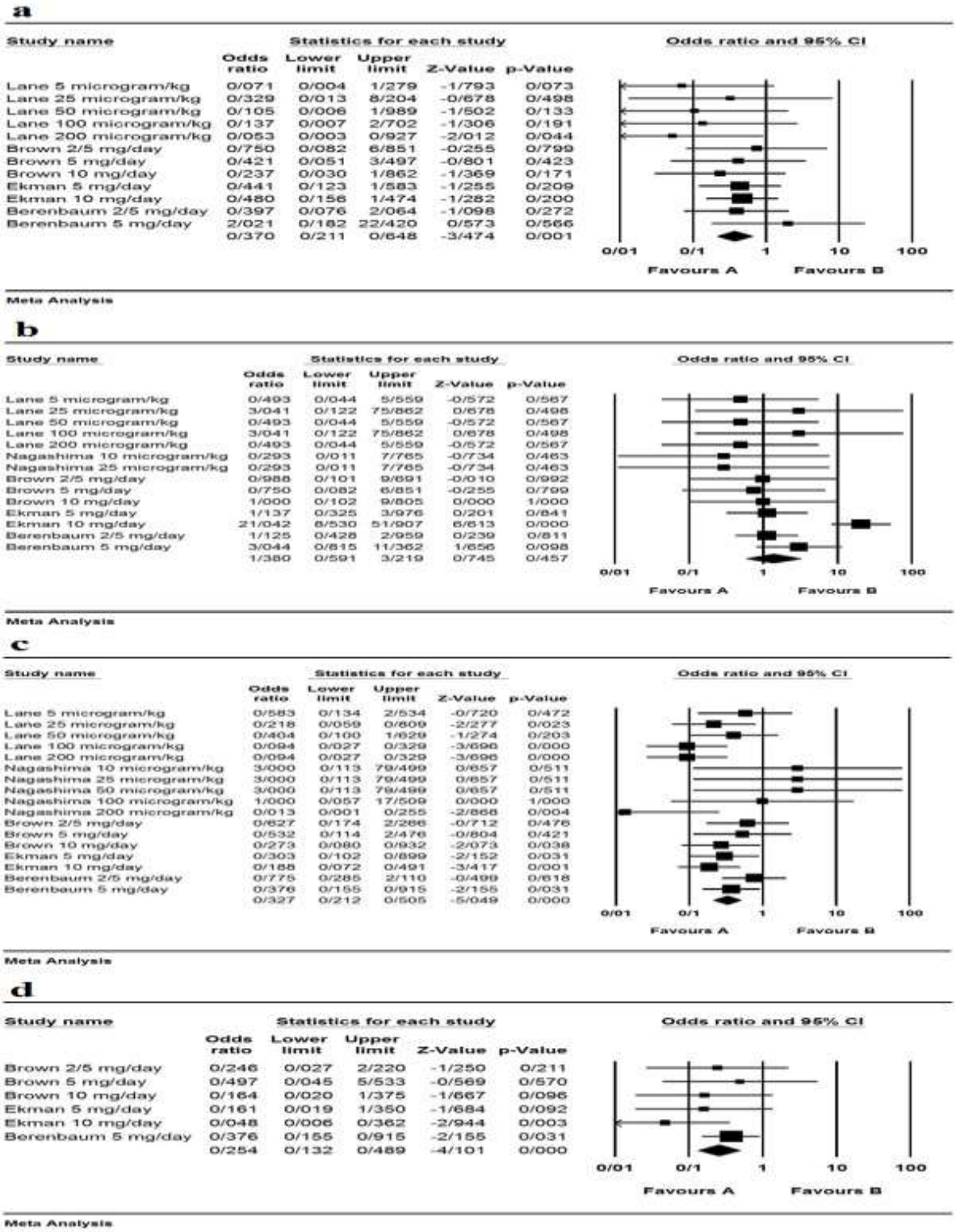

Figure 4. Forest plots of the included studies comparing discontinuations due to adverse events (a), serious adverse events (b), abnormal peripheral sensations (c), and peripheral neuropathy (d) in patients who received tanezumab and placebo.

Although that finding was consistent with our research, that study was intended to investigate the efficacy and safety of tanezumab for patients with OA of the hip or the knee. Thus, we could not determine that tanezumab was certain to have significant influences on the WOMAC pain, the WOMAC physical function and PGA among only patients with knee OA. Therefore, more large scale trials are required to verify 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 roles 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 associated with a significant reduction in pain and improvement in physical function at 3 months; and diclofenac was associated with a significant decrease in pain and improvement in physical function at 3 months. In a meta-analysis investigating the relative efficacies of NSAID therapies compared with that of a placebo, all NSAIDs were shown to reduce pain (19). Although both NSAIDs and tanezumab improve pain, tanezumab is different from NSAIDs regarding its effects on pain relief. This may be because tanezumab specifically inhibits the activation of TrkA by NGF, rather than blocking the cyclooxygenase pathways (10, 20). Both experimental and clinical studies have demonstrated that NGF playes a pivotal role in the generation and maintenance of pain (10, 21). In humans, there were elevated NGF levels found in the synovial fluid of patients with inflammatory, rheumatoid arthritis or osteoarthritis (22). Furthermore, inhibition of NGF action remarkably reduced hyperalgesia and pain perception in animal models with acute local inflammation, chronic inflammatory arthritis or osteoarthritis (23). Regarding the safety of tanezumab, the current meta-analysis showed a significantly increased risk of discontinuations due to adverse events, abnormal peripheral sensations, and peripheral neuropathy. Some discontinuations were thought to be unrelated to the study drug (16). No significant differences in serious adverse events were found between tanezumab and a placebo. Serious adverse events reported in the studies included appendicitis, bacterial arthritis, cellulitis, spinal stenosis, breast cancer, syncope, inguinal hernia, atrioventricular block, and contusion, although some of them were considered to be irrelevant to tanezumab. There are some highlights of the present meta-analysis. Our meta-analysis was performed and analyzed in conformity with the best practice methods recommended by the Cochrane Collaboration (24). A thorough literature search, including PubMed, EMBASE, and CENTRAL, was performed without language restriction. We applied strict and broad inclusion criteria to identify all of the eligible randomized controlled trials in this field. Two investigators independently appraised the risk of bias of the individual studies and assessed the quality of the evidence according to the GRADE approach.

Our meta-analysis also has several potential limitations that should be taken into account when considering the benefits. First, our analysis comprised 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 to overestimate the intervention effect (25), which limits the power of inference. Second, we could not evaluate the potential risk of publication bias due to the small number of included studies, although we deemed our literature search to be exhaustive. Meanwhile, the limited number of studies may also have influenced our conclusions. Furthermore, the follow-up of participants in the included studies was limited. Participants were followed up ranging from 13 to 32 weeks after the initial dose of tanezumab. This may have led to an underestimation of adverse events. Finally, all of the studies were sponsored by pharmaceutical companies. This may also have an influence on the robustness of our conclusions.

Conclusions

In conclusion, the present meta-analysis demonstrated that tanezumab can alleviate pain and improve function. Furthermore, tanezumab was not associated with a significantly increased incidence of serious adverse events but was associated with significant increases in discontinuations due to adverse events, abnormal peripheral sensations and peripheral neuropathy. Considering the limited number of studies, the conclusion should be interpreted cautiously, and more clinical randomized controlled trials are needed to verify 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, writing draft of study.

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

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

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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.

References

1. Dantas LO, Salvini TF, McAlindon TE. Knee osteoarthritis: key treatments and implications for physical therapy. Brazilian journal of physical therapy. 2020.
2. Migliorini F, Driessen A, Oliva F, Maffulli GD, Tingart M, Maffulli N. Better outcomes and reduced failures for arthroplasty over osteotomy for advanced compartmental knee osteoarthritis in patients older than 50 years. Journal of orthopaedic surgery and research. 2020;15(1):545.
3. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014;73(7):1323-30.
4. Arden NK, Perry TA, Bannuru RR, Bruyère O, Cooper C, Haugen IK, et al. Non-surgical management of knee osteoarthritis: comparison of ESCEO and OARSI 2019 guidelines. Nature reviews Rheumatology. 2020.
5. Billesberger LM, Fisher KM, Qadri YJ, Boortz-Marx RL. Procedural Treatments for Knee Osteoarthritis: A Review of Current Injectable Therapies. Pain research & management. 2020;2020:3873098.
6. Cao P, Li Y, Tang Y, Ding C, Hunter DJ. Pharmacotherapy for knee osteoarthritis: current and emerging therapies. Expert opinion on pharmacotherapy. 2020;21(7):797-809.
7. Whelton A. Renal and related cardiovascular effects of conventional and COX-2-specific NSAIDs and non-NSAID analgesics. American journal of therapeutics. 2000;7(2):63-74.
8. Watson JJ, Allen SJ, Dawbarn D. Targeting nerve growth factor in pain: what is the therapeutic potential? BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy. 2008;22(6):349-59.
9. Schnitzer TJ, Lane NE, Birbara C, Smith MD, Simpson SL, Brown MT. Long-term open-label study of tanezumab for moderate to severe osteoarthritic knee pain. Osteoarthritis Cartilage. 2011;19(6):639-46.
10. Hefti F. Pharmacology of nerve growth factor and discovery of tanezumab, an anti-nerve growth factor antibody and pain therapeutic. Pharmacological research. 2020;154:104240.
11. Lane NE, Schnitzer TJ, Birbara CA, Mokhtarani M, Shelton DL, Smith MD, et al. Tanezumab for the treatment of pain from osteoarthritis of the knee. The New England journal of medicine. 2010;363(16):1521-31.
12. Schnitzer TJ, Marks JA. A systematic review of the efficacy and general safety of antibodies to NGF in the treatment of OA of the hip or knee. Osteoarthritis Cartilage. 2015;23 Suppl 1:S8-17.
13. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine. 2009;6(7):e1000097.
14. Ekman EF, Gimbel JS, Bello AE, Smith MD, Keller DS, Annis KM, et al. Efficacy and safety of intravenous tanezumab for the symptomatic treatment of osteoarthritis: 2 randomized controlled trials versus naproxen. The Journal of rheumatology. 2014;41(11):2249-59.
15. Nagashima H, Suzuki M, Araki S, Yamabe T, Muto C. Preliminary assessment of the safety and efficacy of tanezumab in Japanese patients with moderate to severe osteoarthritis of the knee: a randomized, double-blind, dose-escalation, placebo-controlled study. Osteoarthritis Cartilage. 2011;19(12):1405-12.
16. Brown MT, Murphy FT, Radin DM, Davignon I, Smith MD, West CR. Tanezumab reduces osteoarthritic knee pain: results of a randomized, double-blind, placebo-controlled phase

III trial. The journal of pain : official journal of the American Pain Society. 2012;13(8):790-8.
17. Amirfeyz R, Leslie I. AAOS (American Academy of Orthopaedic Surgeons) Clinical Practice Guideline. Treatment of carpal tunnel syndrome. Orthopaedics and Trauma. 2011;25(1):78.
18. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Annals of internal medicine. 2015;162(1):46-54.
19. Bjordal JM, Ljunggren AE, Klovning A, Slørdal L. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. BMJ (Clinical research ed). 2004;329(7478):1317.
20. Webb MP, Helander EM, Menard BL, Urman RD, Kaye AD. Tanezumab: a selective humanized mAb for chronic lower back pain. Therapeutics and clinical risk management. 2018;14:361-7.
21. Miller RE, Malfait AM, Block JA. Current status of nerve growth factor antibodies for the treatment of osteoarthritis pain. Clin Exp Rheumatol. 2017;35 Suppl 107(5):85-7.
22. Seidel MF, Herguijuela M, Forkert R, Otten U. Nerve growth factor in rheumatic diseases. Seminars in arthritis and rheumatism. 2010;40(2):109-26.
23. Miller RE, Block JA, Malfait AM. Nerve growth factor blockade for the management of osteoarthritis pain: what can we learn from clinical trials and preclinical models? Current opinion in rheumatology. 2017;29(1):110-8.
24. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ (Clinical research ed). 2008;336(7650):924-6.
25. Zhang Z, Xu X, Ni H. Small studies may overestimate the effect sizes in critical care meta-analyses: a meta-epidemiological study. Critical care (London, England). 2013;17(1):R2.