Efficacy and Safety of Anti–Nerve Growth Factor Antibody Therapy for Hip and Knee Osteoarthritis

A Meta-analysis

Yijie Gao,* MMed, Zhengxu Hu,† MMed, Yi Huang,* MMed, Weijian Liu,* MMed, and Changle Ren,*‡ MD

Investigation performed at Dalian Municipal Central Hospital, Dalian Medical University, Dalian, China

Background: The efficacy and safety of anti–nerve growth factor (NGF) antibody therapy used for osteoarthritis (OA) pain are controversial.

Purpose: To evaluate the efficacy and safety of anti-NGF antibody therapy via a meta-analysis of randomized controlled trials (RCTs).

Study Design: Systematic review; Level of evidence, 1.

Methods: PubMed, the Cochrane Central Register of Controlled Trials, Embase, and the Web of Science databases were searched for RCTs assessing anti-NGF antibody treatments for hip and knee OA. A total of 623 records were retrieved from the databases. A random-effects model was used to assess primary and secondary outcomes. Bias was assessed using the Cochrane Collaboration tool, funnel plots, and the Egger test. Subgroup analyses were used to assess the efficacy and safety of the independent variables. Sensitivity analysis was conducted to evaluate the effectiveness of tanezumab and the effectiveness of anti-NGF antibodies compared to active comparator drugs. We present the effects of dose, administration mode, and treatment duration on the efficacy and safety of anti-NGF antibody therapy.

Results: There were 19 RCTs included in our meta-analysis. Anti-NGF antibody treatment showed significant improvements on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for pain, physical function, and stiffness as well as on a patient global assessment (PGA). The overall standardized mean differences were as follows: WOMAC pain (–0.31 [95% CI, –0.36 to –0.26]; Z = 11.75; P < .001; I² = 38%), WOMAC physical function (–0.36 [95% CI, –0.41 to –0.30]; Z = 12.67; P < .001; I² = 44%), WOMAC stiffness (–3.59 [95% CI, –4.87 to –2.30]; Z = 5.47; P < .001; I² = 98%), and PGA (–0.28 [95% CI, –0.34 to –0.22]; Z = 9.39; P < .001; I² = 0%). Anti-NGF antibody treatment resulted in a greater incidence of adverse events (risk ratio, 1.09 [95% CI, 1.06 to 1.12]; Z = 5.60; P < .001; I² = 0%). The incidence of serious adverse events was similar between the treatment and control groups (risk ratio, 1.15 [95% CI, 0.98 to 1.34]; Z = 1.71; P = .09; I² = 0%).

Conclusion: Anti-NGF antibody treatment significantly relieved pain and improved function in patients with hip and knee OA. However, no conclusion could be drawn regarding the optimal treatment plan for anti-NGF antibodies when all 3 variables (dose, administration mode, and treatment duration) were combined in the analyses.

Keywords: anti-NGF antibody; osteoarthritis; RCTs; meta-analysis

Osteoarthritis (OA) affects approximately 250 million people worldwide and is a major cause of pain and disability among older adults.20,22 OA is a burden on both individual persons and developed countries, with an effect representing 1.0% to 2.5% of the average gross domestic product.15,20,31

Joint pain and stiffness are the most common symptoms of OA in patients.20 Most guidelines recommend a combination of nonpharmacological and analgesic treatments for OA symptoms.15,21,25 Nonsteroidal anti-inflammatory drugs (NSAIDs) are highly recommended.25 Because NSAIDs may cause side effects, safety is important when choosing treatments for OA.20

Nerve growth factor (NGF) is an essential protein for the growth and maintenance of sympathetic and sensory nerves28 and plays a role in the modulation of nociceptive

The Orthopaedic Journal of Sports Medicine, 10(4), 23259671221088590
DOI: 10.1177/23259671221088590
© The Author(s) 2022

This open-access article is published and distributed under the Creative Commons Attribution · NonCommercial · No Derivatives License (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits the noncommercial use, distribution, and reproduction of the article in any medium, provided the original author and source are credited. You may not alter, transform, or build upon this article without the permission of the Author(s). For article reuse guidelines, please visit SAGE’s website at http://www.sagepub.com/journals-permissions.
sensitization.\textsuperscript{11} Inflamed tissues resulting from arthritis increase the expression of NGF, thus increasing pain sensation.\textsuperscript{8,23,42,41} Anti-NGF antibodies have reduced pain-related behaviors in arthritis animal models,\textsuperscript{42} providing support for anti-NGF antibody therapy for OA pain in humans.\textsuperscript{16} NGF inhibitors in the advanced phases of development for OA include tanezumab, fasinumab, and fulranumab. Tanezumab is a human immunoglobulin G2 monoclonal anti-NGF antibody that blocks the interaction of NGF with its receptors tropomyosin receptor kinase A (TrkA) and p75.\textsuperscript{1} Fasinumab is a fully human high-affinity monoclonal anti-NGF antibody \textsuperscript{41}; fasinumab has a subpicomolar binding affinity for NGF and does not detectably bind to most other members of the neurotrophin family, including brain-derived neurotrophic factor and neurotrophin-3.\textsuperscript{41} Fulranumab is a human recombinant immunoglobulin G2 monoclonal anti-NGF antibody that specifically neutralizes the biological actions of NGF.\textsuperscript{32}

Although meta-analyses of anti-NGF antibody therapy for relieving OA pain have been published,\textsuperscript{9,36,37,44} the appropriate dose, administration mode, and treatment duration have not been assessed. The purpose of this study was to present a meta-analysis assessing dose, administration mode, and treatment duration on the efficacy and safety of anti-NGF antibodies for the treatment of hip and knee OA.

METHODS

Search Strategy

This meta-analysis was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines,\textsuperscript{30} and the study protocol was registered with PROSPERO (registration identification CRD42021242967). We searched for relevant double-blind randomized controlled trials (RCTs) in PubMed, Embase, the Web of Science, and the Cochrane Central Register of Controlled Trials databases between inception and March 21, 2021, using a detailed search strategy (Appendix 1). There were no language restrictions.

Inclusion Criteria

The inclusion criteria were as follows: (1) full-text RCT articles; (2) patients with OA of the knee or hip according to the American College of Rheumatology criteria, ranked grade \( \geq 2 \) according to the Kellgren-Lawrence classification for OA severity; (3) administration of anti-NGF antibodies at any dose versus a placebo or active comparator drug (if both a placebo and active comparator drug were used, only the placebo results were included in the analysis); (4) outcomes of the standardized mean difference (SMD) or mean difference between baseline and the endpoint in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; pain, physical function, and/or stiffness subscales) and patient global assessment (PGA) scores; and (5) safety data (including the incidence of adverse events [AEs] and serious AEs [SAEs]).

Data Extraction

There were 2 investigators (Y.G. and Z.H.) who independently extracted data from RCTs including the study name, pain condition, sample size, mean age of participants, percentage of included women, content of the experimental and control interventions, and outcomes. When the same research appeared in different articles, only the most complete set of data was selected. Disagreements were arbitrated by a third investigator (Y.H.). The SMDs for outcomes between baseline and the endpoint were pooled. If the mean, standard deviation (SD), or standard error of the mean were not obtainable from the text, values were extracted from diagrams and tables.

Numeric values that were only available from graphs or charts were extracted using GetData Graph Digitizer (Version 2.26; https://apps.automeris.io/wpd/index.zh_CN.html). When only the standard error of the mean was reported, the SD was estimated using the equation \( SD = SE \times \sqrt{n} \), where \( n \) is the number of patients. SE, standard error.

Quality and Risk-of-Bias Assessments

The quality of the RCTs was independently evaluated by 2 investigators (Y.G. and Z.H.) using the Cochrane Collaboration tool, funnel plots, and the Egger test for assessing the risk of bias.\textsuperscript{13} A judgment of “yes” indicated a low risk of bias, “no” indicated a high risk of bias, and “unclear” indicated an unclear or unknown risk of bias. When the same research appeared in different articles, only the most complete set of data was selected. The remaining duplicate data were eliminated. Any disagreements regarding data extraction and quality assessment between the 2 investigators were resolved via a consensus or, if necessary, by a third investigator (Y.H.).

Data and Statistical Analyses

The meta-analysis was performed using Review Manager (Version 5.4; Cochrane) and Stata (Version 16.0; Stata-Corp). SMD changes from baseline to the endpoint in WOMAC scores (pain, physical function, and stiffness) and
PGA scores were determined. Secondary outcomes were the incidences of AEs and SAEs. Control groups used either a placebo or active comparator drug. In studies that included results from both placebos and active comparator drugs, only placebo results were extracted.

We conducted subgroup analyses to assess the effects of anti-NGF antibody dose, administration mode, and treatment duration on efficacy and safety. A sensitivity analysis was performed on RCTs that assessed fixed-dose tanezumab. Data from RCTs comparing anti-NGF antibodies and active comparator drugs were extracted separately for the sensitivity analysis.

Continuous outcomes are presented as SMDs with 95% CIs, and dichotomous data are presented as risk ratios (RRs) with 95% CIs. A random-effects model was used to assess variations in the meta-analysis characteristics. Heterogeneity was determined using the $I^2$ statistic. The significance of pooled effects was evaluated via the $Z$ test. The threshold of significance was set at $P < .05$.

RESULTS

Study Characteristics

A total of 623 records were retrieved from the databases. Of these, 47 RCTs met initial eligibility criteria. Ultimately, 19 double-blind RCTs§ were included in this meta-analysis (Figure 1).

The characteristics of the included RCTs are shown in Table 1. The RCTs were double-blind, parallel-group, and placebo or active comparator drug–controlled studies. In the 19 RCTs, 13 used tanezumab, 4 used fulranumab, and 2 used fasinumab. In addition, 10 included only intravenous (IV) injections, 8 included only subcutaneous (SC) injections, and 1 included both modes. There were 4 studies that included active comparator drug controls, and 6 studies reported outcomes at 8 weeks.

Most of the RCTs used fixed-dose drugs, but 3 studies used weight-adjusted drugs. According to the methods of a previous meta-analysis, the classification of drug metering in the literature, and a comparison of drug doses in different studies, we divided drug doses into 3 levels. The low-dose subgroup included tanezumab (10 μg/kg, 25 μg/kg, and 2.5 mg), fulranumab (1 mg every 4 weeks and 3 mg every 8 weeks), and fasinumab (0.03 mg/kg, 1 mg, and 3 mg). The moderate-dose subgroup included tanezumab (50 μg/kg and 5 mg), fulranumab (3 mg every 4 weeks and 6 mg every 8 weeks), and fasinumab (0.1 mg/kg and 6 mg). The high-dose subgroup included tanezumab (100 μg/kg, 200 μg/kg, and 10 mg), fulranumab (10 mg every 8 weeks), and fasinumab (0.3 mg/kg and 9 mg).

### References

1. References 2–7, 10, 14, 18, 23, 26, 27, 29, 32–35, 40, 41.
2. References 2, 3, 4, 5, 6, 7, 14, 18, 26, 29, 34, 35, 40.
3. References 2, 5, 6, 7, 14, 26, 29, 35, 40, 41.
## TABLE 1
Characteristics of Included Studies<sup>a</sup>

| Lead Author (Year) | Type of OA | Sample Size, n | Female Sex, % | Patient Age, y | Outcomes |
|--------------------|------------|----------------|----------------|----------------|-----------|
| Lane<sup>26</sup> (2010) | Knee | 444 | 59.0 | | PGA, WOMAC (pain, physical function, stiffness), AEs, SAEs |
| | | | | | |
| Brown<sup>7</sup> (2012) | Knee | 690 | 60.9 | | PGA, WOMAC (pain, physical function), AEs, SAEs |
| | | | | | |
| Nagashima<sup>29</sup> (2011) | Knee | 83 | 68.7 | | WOMAC (pain, physical function, stiffness), AEs, SAEs |
| | | | | | |
| Brown<sup>5</sup> (2013) | Knee | 621 | 61.8 | | PGA, WOMAC (pain, physical function), AEs, SAEs |
| | | | | | |
| Spierings<sup>40</sup> (2013) | Knee or hip | 610 | 62.5 | | PGA, WOMAC (pain, physical function, stiffness), AEs, SAEs |
| | | | | | |
| Balanescu<sup>2</sup> (2014) | Knee or hip | 604 | 77.6 | | PGA, WOMAC (pain, physical function), AEs, SAEs |
| | | | | | |
| Brown<sup>6</sup> (2014) | Knee or hip | 219 | 59.4 | | AEs, SAEs |
| | | | | | |
| Ekman<sup>14</sup> (2014) | Knee or hip | 1668 | 61.9 | | PGA, WOMAC (pain, physical function), AEs, SAEs |
| Study 1015 | | | | | |
| | Tanezumab IV (5 mg q8wk): 61.1 ± 10.1 | | | | |
| | Tanezumab IV (10 mg q8wk): 61.1 ± 10.3 | | | | |
| | Naproxen oral (500 mg BID): 61.4 ± 10.0 | | | | |
| | Placebo: 60.9 ± 10.1 | | | | |
| Study 1018 | | | | | |
| | Tanezumab IV (5 mg q8wk): 59.8 ± 9.6 | | | | |
| | Tanezumab IV (10 mg q8wk): 59.2 ± 10.3 | | | | |
| | Naproxen oral (500 mg BID): 60.3 ± 10.5 | | | | |
| | Placebo: 60.1 ± 9.4 | | | | |
| Tiseo<sup>41</sup> (2014) | Knee | 215 | 68.8 | | WOMAC (pain, physical function), AEs |
| | | | | | |
| Schnitzer<sup>35</sup> (2015) | Knee or hip | 2700 | 70.5 | | PGA, WOMAC (pain, physical function), AEs, SAEs |
| | | | | | |
| Mayorga<sup>27</sup> (2016) | Knee or hip | 196 | 56.1 | | PGA, WOMAC (pain, physical function, stiffness), AEs, SAEs |

(continued)
The Orthopaedic Journal of Sports Medicine

Efficacy and Safety of Anti-NGF Antibody Therapy

Table 1 (continued)

| Lead Author (Year) | Type of OA | Sample Size, n | Female Sex, % | Patient Age, y | Outcomes |
|--------------------|------------|----------------|---------------|----------------|----------|
| Sanga23 (2017)     | Knee or hip | 401            | 59.0          | 61.0           | Fulranumab SC (1 mg q4wk): 60.8 ± 9.19; Fulranumab SC (3 mg q8wk): 60.7 ± 8.80; Fulranumab SC (6 mg q8wk): 60.9 ± 9.33; Fulranumab SC (10 mg q8wk): 62.2 ± 9.59; Placebo: 61.0 ± 8.29; WOMAC (pain, physical function), AEs, SAEs |
| Birbara4 (2018)    | Knee or hip | 1057           | 66.5          | 62.0           | Tanezumab SC (2.5 mg q8wk): 61.0; Tanezumab SC (5 mg q8wk): 60.3; Tanezumab SC (10 mg q8wk): 58.2; Tanezumab IV (10 mg q8wk): 59.6; WOMAC (pain, physical function), AEs, SAEs |
| Kelly23 (2019)     | Knee or hip | 419            | 64.6          | 61.5 ± 7.8     | Paseinumab SC (1 mg q4wk): 60.7 ± 8.9; Paseinumab SC (3 mg q4wk): 60.7 ± 8.9; Paseinumab SC (6 mg q4wk): 60.1 ± 7.9; Paseinumab SC (9 mg q4wk): 61.5 ± 7.8; Placebo: 60.1 ± 7.2; WOMAC (pain, physical function), AEs |
| Dakin10 (2019)     | Knee or hip | 245            | 62.0          | 62.0 ± 10.14   | Fulranumab SC (1 mg q4wk): 62.0 ± 10.14; Fulranumab SC (3 mg q4wk): 63.0 ± 9.59; Placebo: 64.4 ± 8.63; WOMAC (pain), AEs, SAEs |
| Schnitzer34 (2019) | Knee or hip | 696            | 65.1          | 60.9 ± 7.2     | Tanezumab SC (2.5 mg): 60.9; Tanezumab SC (2.5 mg/5 mg): 61.2; Placebo: 60.4; WOMAC (pain, physical function), AEs, SAEs |
| Berenbaum3 (2020)  | Knee or hip | 849            | 69.1          | 65.2 ± 10.2    | Tanezumab SC (2.5 mg q8wk): 65.2 ± 8.4; Tanezumab SC (5 mg q8wk): 65.2 ± 10.2; Placebo: 64.2 ± 9.6; WOMAC (pain, physical function), AEs, SAEs |
| Hochberg18 (2021)  | Knee or hip | 2996           | 65.2          | 60.3 ± 9.2     | Tanezumab SC (2.5 mg q8wk): 60.3 ± 9.2; Tanezumab SC (5 mg q8wk): 61.2 ± 9.6; Open-label NSAID oral: 60.3 ± 9.5; WOMAC (pain, physical function), AEs, SAEs |

The results demonstrated a significant decrease in pain (SMD, –0.31 [95% CI, –0.36 to –0.26]; Z = 11.75; P < .00001; I^2 = 38%). There were 9 studies that reported only intravenous (IV) administration.††7 that reported only subcutaneous (SC) administration,3,10,18,23,27,33,34 and 1 that reported both administration modes.4 The WOMAC pain score was reported at 8 weeks in 6 studies,2,4,14,29,40,41 at 16 weeks in 13 studies,‡‡ and at 24 weeks in 1 study.3 To directly compare the effects of dose, administration mode and treatment duration combined on the outcome indicators, we divided the RCTs into 14 subgroups. The results are shown in Table 2 and Appendix 2 (Figure A1). The results of the subgroup analysis showed that the IV administration of a high-dose anti-NGF over a period of 16 weeks significantly improved the WOMAC pain score (SMD = –0.42; [95% CI, −0.55 to –0.28]; Z = 5.99; P < .00001; I^2 = 55%).

TABLE 2

Subgroup Analysis of WOMAC Pain Scores According to Dose, Administration Mode, and Treatment Duration†

| Dose/Mode/Duration | SMD (95% CI) | Z Value | P Value | I² Value |
|--------------------|--------------|---------|---------|----------|
| Low/IV/16 wk       | –0.39 (–0.62 to –0.17) | 3.42 | .0006 | 45% |
| Low/IV/8 wk        | –0.22 (–0.48 to 0.05)  | 1.61 | .11  | 0% |
| Low/SC/24 wk       | –0.16 (–0.36 to 0.04)  | 1.53 | .13  | NA |
| Low/SC/16 wk       | –0.08 (–0.17 to 0.01)  | 1.74 | .08  | 0% |
| Low/SC/8 wk        | –0.45 (–0.97 to 0.07)  | 1.71 | .09  | NA |
| Moderate/IV/16 wk  | –0.34 (–0.43 to –0.25) | 7.48 | <.00001 | 0% |
| Moderate/IV/8 wk   | –0.40 (–0.53 to –0.27) | 6.17 | <.00001 | 0% |
| Moderate/SC/24 wk  | –0.21 (–0.41 to –0.01) | 2.02 | .04  | NA |
| Moderate/SC/16 wk  | –0.10 (–0.19 to –0.01) | 2.26 | .02  | 0% |
| Moderate/SC/8 wk   | –0.41 (–0.94 to 0.12)  | 1.51 | .13  | NA |
| High/IV/16 wk      | –0.42 (–0.55 to –0.28) | 5.99 | <.00001 | 55% |
| High/IV/8 wk       | –0.40 (–0.53 to –0.28) | 6.38 | <.00001 | 0% |
| High/SC/16 wk      | –0.23 (–0.58 to 0.12)  | 1.30 | .19  | 20% |
| High/SC/8 wk       | –0.31 (–0.36 to –0.26) | 1.68 | .09  | NA |

†Bolded P values indicate statistical significance (P < .05). IV, intravenous; NA, not applicable; SC, subcutaneous; SMD, standardized mean difference; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

‡‡References 2, 6, 7, 14, 26, 29, 35, 40, 41.

††References 2, 6, 7, 10, 14, 18, 23, 26, 27, 33, 34, 41.
A total of 16 studies§§ were assessed to determine anti-NGF antibody treatment effects based on the WOMAC physical function score (Figure 4). The overall physical function score significantly improved (SMD, –0.36 [95% CI, –0.41 to –0.30]; Z = 12.67; P < .00001; I² = 44%) (Figure 4).

There were 9 studies that reported only IV administration§§§ 6 that reported only SC administration, 3,10,18,27,33,34 and 1 that reported both modes. 4 The WOMAC physical function score was reported at 8 weeks in 6 studies, 2,4,10,14,26,27 at 16 weeks in 12 studies, 5 and at 24 weeks in 1 study. 3 To directly compare the combined effects of dose, administration mode, and treatment duration on the outcome indicators, we divided the RCTs into 14 subgroups. The results are shown in Table 3 and Appendix 2 (Figure A2). The results of the subgroup analysis showed that IV administration of a moderate dose of anti-NGF antibody treatment over a period of 8 weeks significantly improved the WOMAC physical function score (SMD, –0.46 [95% CI, –0.58 to –0.33]; Z = 7.01; P < .00001; I² = 0%).

WOMAC Stiffness Score

A total of 4 studies 26,27,29,40 assessed anti-NGF antibody treatment on WOMAC stiffness scores (Figure 5). The overall stiffness score significantly improved (SMD, –3.59 [95% CI, –4.87 to –2.30]; Z = 5.47; P < .00001; I² = 98%) (Figure 5).

PGA Score

A total of 13 studies## were assessed to determine anti-NGF antibody treatment effects on the PGA score. The overall PGA score significantly improved (SMD, –0.28 [95% CI, –0.34 to –0.22]; Z = 9.39; P < .00001; I² = 50%) (Figure 6).

There were 7 studies that reported only IV administration, 2,6,7,14,26,35,40 5 that reported only SC administration, 3,18,27,33,34 and 1 that reported both modes. 4 PGA scores were reported at 8 weeks in 4 studies, 2,4,14,40 at 16 weeks in 10 studies, 6 and at 24 weeks in 1 study. 3 To directly compare the combined effects of dose, administration mode, and treatment duration on the outcome indicators, we divided the RCTs into 14 subgroups. The results are shown in Table 4 and Appendix 2 (Figure A3). The results of the subgroup analysis showed that IV administration of a moderate dose of anti-NGF antibody treatment over a period of 8 weeks significantly improved the PGA score (SMD, –0.45 [95% CI, –0.58 to –0.31]; Z = 6.63; P < .00001; I² = 0%).

Adverse Events

AEs were reported in all RCTs. Nausea, arthralgia, paresthesia, hypoesthesia, and headache were the most frequently reported AEs in the treatment groups. The overall incidence of patients with AEs was higher in the anti-NGF

§§References 2–4, 6, 7, 10, 14, 18, 26, 27, 29, 33–35, 40, 41.
§§§References 2, 6, 7, 10, 14, 18, 26, 27, 33, 34, 35, 40.
##References 2–4, 6, 7, 10, 14, 18, 26, 27, 33–35, 40.
References 2–7, 10, 14, 18, 23, 26, 27, 29, 32–35, 40, 41.
Figure 3. Forest plot of changes from baseline to the endpoint for the Western Ontario and McMaster Universities Osteoarthritis Index pain score. DSR, diclofenac sustained release; IV, intravenous; IV, inverse variance; q4wk, once every 4 weeks; q8wk, once every 8 weeks; SC, subcutaneous; Std. Mean Difference, standardized mean difference.
Figure 4. Forest plot of changes from baseline to the endpoint for the Western Ontario and McMaster Universities Osteoarthritis Index physical function score. DSR, diclofenac sustained release; IV, intravenous; IV, inverse variance; q4wk, once every 4 weeks; q8wk, once every 8 weeks; SC, subcutaneous; Std. Mean Difference, standardized mean difference.
antibody treatment groups than in the control groups. RR s for AE s were significantly increased (RR, 1.09 [95% CI, 1.06-1.12]; Z = 5.60; P < .00001; I² = 6% (Figure 7).

There were 10 studies that reported only IV administration, 8 that reported only SC administration, 3,10,18,23,27,32,33,34 and 1 that reported both modes.4 To directly compare the combined effects of dose and administration mode on outcome indicators, we divided the RCTs into 6 subgroups. The results are shown in Table 5 and Appendix 2 (Figure A4). The results of the subgroup analysis showed that IV administration of a low dose of anti-NGF antibodies significantly increased the incidence of AEs (RR, 1.20 [95% CI, 1.05-1.55]; Z = 2.44; P = .01; I² = 0%).

Additionally, 17 studies6 were assessed to determine anti-NGF antibody treatment effects on SAES. Increased OA, osteonecrosis, and arthralgia were the most commonly reported SAES in all treatment groups. Compared with the control groups, the incidence of SAES in the anti-NGF antibody treatment groups did not significantly increase (RR, 1.15 [95% CI, 0.98-1.34]; Z = 1.71; P = .09; I² = 0%) (Figure 8).

There were 9 studies that reported only IV administration, 7 that reported only SC administration, and 1 that reported both modes. To directly compare the combined effects of dose and administration mode on the outcome indicators, we divided the RCTs into 6 subgroups. The results are shown in Table 6 and Appendix 2 (Figure A5). The results of the subgroup analysis showed that in all treatment groups, the incidence of SAES did not significantly increase.

Sensitivity Analysis

A sensitivity analysis was performed on 9 RCTs2-7,14,18,35 that assessed fixed-dose tanezumab (Table 7 and Appendix 3). The analysis revealed significant improvements in the overall WOMAC pain score (SMD, –0.27 [95% CI, –0.32 to –0.21]; Z = 9.51; P < .001; I² = 32%), WOMAC physical function score (SMD, –0.31 [95% CI, –0.37 to –0.25]; Z = 10.12; P < .001; I² = 42%), and PGA score (SMD, –0.24 [95% CI, –0.30 to –0.17]; Z = 7.44; P < .001; I² = 47%) (Table 7). The proportion of the fixed-dose tanezumab group that discontinued treatment because of AEs was significantly higher than that of the control group (RR, 1.12 [95% CI, 1.08 to 1.15]; Z = 6.15; P < .001; I² = 0%). Compared with the control group, the incidence of SAES in the fixed-dose tanezumab group did not significantly increase (RR, 1.14 [95% CI, 0.97 to 1.34]; Z = 1.55; P = .12; I² = 0%).

A sensitivity analysis of 4 RCTs with active comparator drugs was performed (Appendix 4). There were 2 RCTs27,40 that used controlled-release oxycodone and 2 RCTs14,18 that used NSAIDs as active comparator drug controls. There were significant improvements in the WOMAC pain score (SMD, –0.21 [95% CI, –0.31 to –0.11]; Z = 3.99; P < .001; I² = 54%), WOMAC physical function score (SMD, –0.24 [95% CI, –0.34 to –0.13]; Z = 4.40; P < .001; I² = 56%), and PGA score (SMD, –0.20 [95% CI, –0.32 to –0.09]; Z = 3.45; P = .0006; I² = 63%). The results of the sensitivity analysis showed that there was no significant difference in the rate of treatment discontinuation due to AEs between the Anti-NGF antibody group and the active comparator drugs group (RR, 0.94 [95% CI, 0.85 to 1.04]; Z = 1.14; P = .26; I² = 73%). Compared with the control group, the incidence of SAES in the fixed-dose tanezumab group did not significantly increase (RR, 1.20 [95% CI, 0.90 to 1.61]; Z = 1.22; P = .22; I² = 9%).

Publication Bias

Asymmetry in the funnel plots indicated a publication bias (Figure 9). The P value from the Egger test13 was <.001 for the WOMAC pain score, indicating an inflation of SMD values due to publication bias.

DISCUSSION

According to our results, anti-NGF antibody therapy was an effective type of treatment for OA. The pooled results showed a significant reduction in the change in WOMAC pain (SMD, –0.31 [95% CI, –0.36 to –0.26]; Z = 11.75; P < .00001; I² = 38%), WOMAC physical function (SMD, –0.36 [95% CI, –0.41 to –0.30]; Z = 12.67; P < .00001; I² = 44%), WOMAC stiffness (SMD, –3.59 [95% CI, –4.87 to –2.30]; Z = 5.47; P < .00001; I² = 98%), and PGA scores (SMD, –0.28 [95% CI, –0.34 to –0.22]; Z = 9.39; P < .00001; I² = 50%). In contrast to good treatment effects, the incidence of AEs also increased (RR, 1.09 [95% CI, 1.06 to 1.12]; Z = 5.60; P < .00001; I² = 0%).

There have been reports on the use of the anti-NGF antibodies tanezumab, fulranumab, and fasidinumab to treat hip and/or knee OA pain.10,18,35 However, there is still

### Table 3

Subgroup Analysis of WOMAC Physical Function Scores According to Dose, Administration Mode, and Treatment Duration

| Dose/Mode/Duration | SMD (95% CI) | Value | P Value | F Value |
|--------------------|-------------|-------|---------|---------|
| Low/IV/16 wk       | –0.37 (–0.60 to –0.14) | 3.12   | .002    | 71%     |
| Low/IV/8 wk        | –0.22 (–0.48 to 0.05)  | 1.61   | .11      | 0%      |
| Low/SC/24 wk       | –0.22 (–0.42 to –0.02)  | 2.12   | .03      | NA      |
| Low/SC/16 wk       | –0.24 (–0.41 to –0.06)  | 2.64   | .008     | 0%      |
| Low/SC/8 wk        | –0.42 (–0.94 to 0.10)   | 1.59   | .11      | NA      |
| Moderate/IV/16 wk  | –0.36 (–0.45 to –0.27)  | 8.01   | <.00001  | 0%      |
| Moderate/IV/8 wk   | –0.46 (–0.58 to –0.33)  | 7.01   | <.00001  | 0%      |
| Moderate/SC/24 wk  | –0.24 (–0.45 to –0.04)  | 2.35   | .02      | NA      |
| Moderate/SC/16 wk  | –0.13 (–0.22 to –0.03)  | 2.70   | .007     | 0%      |
| Moderate/SC/8 wk   | –0.41 (–0.93 to 0.12)   | 1.51   | .13      | NA      |
| High/IV/16 wk      | –0.44 (–0.59 to –0.30)  | 5.95   | <.00001  | 60%     |
| High/IV/8 wk       | –0.44 (–0.57 to –0.32)  | 6.99   | <.00001  | 0%      |
| High/SC/16 wk      | –0.30 (–0.62 to 0.02)   | 1.84   | .07      | 6%      |
| High/SC/8 wk       | –0.36 (–0.41 to –0.30)  | 3.46   | <.00001  | NA      |

*Bolded P values indicate statistical significance (P < .05). IV, intravenous; NA, not applicable; SC, subcutaneous; SMD, standardized mean difference; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.*

References 2, 5, 6, 7, 14, 26, 29, 35, 40, 41

References 2–7, 14, 18, 23, 26, 27, 29, 32–35, 40.
Figure 5. Forest plot of changes from baseline to the endpoint for the Western Ontario and McMaster Universities Osteoarthritis Index–stiffness score.

| Study or Subgroup | Lane 2010 Tanezumab 50 μg/kg IV [34] | Lane 2010 Tanezumab 150 μg/kg IV [34] | Lane 2010 Tanezumab 300 μg/kg IV [34] | Lane 2010 Tanezumab 100 μg/kg SC [34] | Lane 2010 Tanezumab 50 μg/kg IV [34] | Lane 2010 Tanezumab 100 μg/kg SC [34] | Lane 2010 Tanezumab 200 μg/kg IV [34] | Lane 2010 Tanezumab 100 μg/kg SC [34] | Lane 2010 Tanezumab 50 μg/kg IV [34] | Lane 2010 Tanezumab 100 μg/kg SC [34] | Lane 2010 Tanezumab 200 μg/kg IV [34] | Lane 2010 Tanezumab 100 μg/kg SC [34] | Lane 2010 Tanezumab 50 μg/kg IV [34] | Lane 2010 Tanezumab 100 μg/kg SC [34] |
|-------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|
| Mean              | -17.6 ± 14.42                        | -21.42 ± 14.42                       | -16.3 ± 14.42                         | -21.42 ± 14.42                       | -16.3 ± 14.42                         | -21.42 ± 14.42                       | -16.3 ± 14.42                         | -21.42 ± 14.42                       | -16.3 ± 14.42                         | -21.42 ± 14.42                       | -16.3 ± 14.42                         | -21.42 ± 14.42                       | -16.3 ± 14.42                         | -21.42 ± 14.42                       |
| SD                | 72 ± 9.2                             | 72 ± 9.2                             | 72 ± 9.2                              | 72 ± 9.2                              | 72 ± 9.2                              | 72 ± 9.2                              | 72 ± 9.2                              | 72 ± 9.2                              | 72 ± 9.2                              | 72 ± 9.2                              | 72 ± 9.2                              | 72 ± 9.2                              | 72 ± 9.2                              | 72 ± 9.2                              |
| Control Mean      | 15                                   | 15                                   | 15                                    | 15                                    | 15                                    | 15                                    | 15                                    | 15                                    | 15                                    | 15                                    | 15                                    | 15                                    | 15                                    | 15                                    |
| Control SD        | 15 ± 0.9                             | 15 ± 0.9                             | 15 ± 0.9                              | 15 ± 0.9                              | 15 ± 0.9                              | 15 ± 0.9                              | 15 ± 0.9                              | 15 ± 0.9                              | 15 ± 0.9                              | 15 ± 0.9                              | 15 ± 0.9                              | 15 ± 0.9                              | 15 ± 0.9                              | 15 ± 0.9                              |
| Control Weight    | 100                                   | 100                                   | 100                                   | 100                                   | 100                                   | 100                                   | 100                                   | 100                                   | 100                                   | 100                                   | 100                                   | 100                                   | 100                                   | 100                                   |
| IV Random. 95% CI | -0.56 [-1.13, -0.00]                  | -0.80 [-1.37, -0.23]                  | -0.80 [-1.37, -0.23]                  | -0.80 [-1.37, -0.23]                  | -0.80 [-1.37, -0.23]                  | -0.80 [-1.37, -0.23]                  | -0.80 [-1.37, -0.23]                  | -0.80 [-1.37, -0.23]                  | -0.80 [-1.37, -0.23]                  | -0.80 [-1.37, -0.23]                  | -0.80 [-1.37, -0.23]                  | -0.80 [-1.37, -0.23]                  | -0.80 [-1.37, -0.23]                  | -0.80 [-1.37, -0.23]                  |

Figure 6. Forest plot of changes from baseline to the endpoint for the patient global assessment score. DSR, diclofenac sustained release; IV, intravenous; IV, inverse variance; q4wk, once every 4 weeks; q8wk, once every 8 weeks; SC, subcutaneous; Std. Mean Difference, standardized mean difference.
controversy over the effectiveness and safety of this treatment. The optimal dose, administration mode, and treatment duration of each drug have not been determined for this therapy in a clinical setting.

The therapeutic effects and safety of anti-NGF antibody treatment from 19 RCTs were assessed for hip and knee OA pain. Pooled results showed significant reductions in WOMAC scores for pain, physical function, and stiffness as well as in PGA scores. These changes show the clinical significance of anti-NGF antibody treatment for hip and/or knee OA. The results are consistent with previous RCTs indicating that anti-NGF antibody drugs have a significant effect on pain relief and functional improvement in patients with hip and/or knee OA. It may be that NGF plays a key role in the process of pain generation under chronic pain conditions. Anti-NGF antibodies have the potential to normalize noxious hyperactivity and produce pain relief in a clinical environment. These drugs may reduce the concentration of free NGF, prevent NGF from binding to TrkA, or prevent TrkA from being activated and reduce the concentration of free NGF, preventing NGF from binding to TrkA, or preventing TrkA from being activated and reduce the concentration of free NGF. Overall, the research quality was high. Most of the studies were sponsored by pharmaceutical companies, which could have an effect on the findings. Our results indicate that a large number of unpublished studies and studies reporting nonsignificant results have led to publication bias.

High doses of anti-NGF antibodies improve OA pain but increase the incidence of AEs. Our meta-analysis focused on the effect of dose, administration mode, and treatment duration on the treatment of OA pain. Our subgroup analysis of the effects of the 3 combined variables showed that there was no unique treatment that achieved an optimal therapeutic effect. High doses of anti-NGF antibodies via IV administration over a 16-week treatment period significantly improved pain scores. Moderate doses of anti-NGF antibodies via IV administration over an 8-week treatment period significantly improved physical function scores. Low doses of anti-NGF antibodies via IV administration over a 16-week treatment period significantly improved PGA scores. In general, the IV administration of anti-NGF antibodies was a more effective treatment method compared to SC administration. Low doses of anti-NGF antibodies had the lowest incidence of AEs using IV administration. Moderate doses of anti-NGF antibodies had the highest incidence of AEs using SC administration. The incidence of AEs in all treatment groups was higher than that in the control groups. An indirect comparison of the incidence of AEs in subgroup analyses showed that the incidence of AEs with SC administration was lower than that of the corresponding dose with IV administration. In all treatment groups, the incidence of SAEs was similar to that in the control groups. This finding is consistent with the results of the direct comparison between the IV and SC administrations of tanezumab.

| Dose/Mode/Duration       | SMD     | (95% CI)      | Z Value | P Value | I² Value |
|--------------------------|---------|---------------|---------|---------|----------|
| Low-dose/IV/16 wk        | −0.42   | (−0.63 to −0.21) | 3.92    | <.0001  | 32%      |
| Low-dose/IV/8 wk         | −0.18   | (−0.50 to 0.13)  | 1.13    | 0.26    | NA       |
| Low-dose/SC/24 wk        | −0.1    | (−0.30 to 0.10)  | 0.96    | 0.34    | NA       |
| Low-dose/SC/16 wk        | −0.05   | (−0.14 to 0.05)  | 1.02    | 0.31    | 0%       |
| Low-dose/SC/8 wk         | −0.3    | (−0.81 to 0.22)  | 1.13    | 0.26    | NA       |
| Moderate-dose/IV/16 wk   | −0.27   | (−0.37 to −0.16) | 4.9     | <.00001 | 27%      |
| Moderate-dose/IV/8 wk    | −0.45   | (−0.58 to −0.31) | 6.63    | <.00001 | 0%       |
| Moderate-dose/SC/24 wk   | −0.18   | (−0.38 to 0.02)  | 1.72    | 0.08    | NA       |
| Moderate-dose/SC/16 wk   | −0.06   | (−0.16 to 0.03)  | 1.32    | 0.19    | 0%       |
| Moderate-dose/SC/8 wk    | −0.19   | (−0.72 to 0.33)  | 0.73    | 0.48    | NA       |
| High-dose/IV/16 wk       | −0.34   | (−0.48 to −0.20) | 4.73    | <.00001 | 57%      |
| High-dose/IV/8 wk        | −0.42   | (−0.54 to −0.29) | 6.34    | <.00001 | 0%       |
| High-dose/SC/16 wk       | −0.13   | (−0.51 to 0.26)  | 0.64    | 0.52    | 0%       |
| High-dose/SC/8 wk        | −0.28   | (−0.79 to 0.23)  | 1.08    | 0.28    | NA       |

*Bolded P values indicate statistical significance (P < .05). IV, intravenous; NA, not applicable; SC, subcutaneous; SMD, standardized mean difference.
Figure 7. Forest plot of differences in adverse event rates between the experimental and control groups. DSR, diclofenac sustained release; IV, intravenous; M-H, random Mantel-Haenszel random-effects model; q4wk, once every 4 weeks; q8wk, once every 8 weeks; SC, subcutaneous.
are consistent with the observation that a higher dose of tanezumab provides improved efficacy,
our findings of the effectiveness of IV administration on treatment outcomes differ from the results of Birbara et al.4 Considering that only one study used a high dose of tanezumab (10 mg) with SC administration,
we believe that additional studies comparing different administration modes should be performed.
Our sensitivity analysis demonstrated that compared with oxycodone,27,40 and NSAIDs,14,18 anti-NGF antibodies significantly improved pain scores, physical function scores, and PGA scores. There was no significant difference in the incidence of AEs for anti-NGF antibodies compared to analgesics.14,18,27,40

**Table 5**
Subgroup Analysis of Adverse Events According to Dose and Administration Mode

| Dose/Mode     | RR (95% CI)  | Z Value | P Value | I² Value |
|---------------|--------------|---------|---------|----------|
| Low/IV        | 1.28 (1.05-1.55) | 2.44    | .01     | 0%       |
| Low/SC        | 1.02 (0.85-1.09) | 0.55    | .58     | 0%       |
| Moderate/IV   | 1.11 (1.04-1.19) | 2.96    | .003    | 0%       |
| Moderate/SC   | 1.08 (1.03-1.14) | 3.01    | .003    | 0%       |
| High/IV       | 1.15 (1.07-1.23) | 4.04    | <.0001  | 0%       |
| High/SC       | 1.00 (0.87-1.14) | 0.05    | .96     | 0%       |

**Bolded** P values indicate statistical significance (P < .05).
IV, intravenous; RR, risk ratios; SC, subcutaneous.

**Figure 8.** Forest plot of differences in serious adverse event rates between the experimental and control groups.
The safety of anti-NGF antibodies has been a concern in clinical applications.17 Our meta-analysis showed that the frequency of drug withdrawal because of AEs in the treatment group was higher than that in the control group and that the incidence of SAEs was similar between the 2 groups. In multiple studies, a lower incidence of AEs in the placebo group or placebo combined with NSAID group compared to the anti-NGF antibody group or anti-NGF antibody combined with NSAID group was reported.2,35 Several studies reported that the frequency of treatment discontinuation because of AEs with anti-NGF antibodies is similar to or lower than the rates observed with NSAIDs.14,27,35,40 Our safety data showed that the incidence of drug withdrawal because of AEs and SAEs meets the prescribed standards.14,27,35,40 We found that anti-NGF antibody treatments are well tolerated and safe.

The most common AEs associated with the use of anti-NGF antibodies include peripheral edema, joint and limb pain, and peripheral neuropathy.12,33,35,41 Less than 10% of patients have neuropathy.12 Symptoms of abnormal peripheral sensation are usually mild to moderate,

**TABLE 6**
Subgroup Analysis of Serious Adverse Events According to Dose and Administration Mode

| Dose/Mode | RR (95% CI) | Z Value | P Value | I² Value |
|-----------|-------------|---------|---------|----------|
| Low/IV    | 1.09 (0.49-2.39) | 0.20  | .84     | 0%       |
| Low/SC    | 0.97 (0.70-1.36) | 0.16  | .88     | 3%       |
| Moderate/IV | 1.10 (0.76-1.60) | 0.50  | .62     | 0%       |
| Moderate/SC | 1.34 (0.99-1.80) | 1.92  | .05     | 2%       |
| High/IV   | 1.12 (0.79-1.59) | 0.61  | .54     | 0%       |
| High/SC   | 1.34 (0.52-3.47) | 0.61  | .54     | 0%       |

*IV, intravenous; RR, risk ratios; SC, subcutaneous.*

**TABLE 7**
Sensitivity Analysis of Fixed-Dose Tanezumab

| Outcome | SMD or RR (95% CI) | Z Value | P Value | I² Value |
|---------|--------------------|---------|---------|----------|
| WOMAC pain |                     |         |         |          |
| Low dose/IV | −0.28 (−0.47 to −0.10) | 3.04  | .002    | 0%       |
| Low dose/SC | −0.11 (−0.21 to −0.01) | 2.06  | .04     | 15%      |
| Moderate dose/IV | −0.33 (−0.42 to −0.24) | 7.47  | <.00001 | 0%       |
| Moderate dose/SC | −0.12 (−0.21 to −0.03) | 2.71  | .007    | 1%       |
| High dose/IV | −0.33 (−0.42 to −0.25) | 7.66  | <.00001 | 0%       |
| High dose/SC | −0.44 (−0.95 to 0.07) | 1.68  | .09     | NA       |
| WOMAC physical function |                     |         |         |          |
| Low dose/IV | −0.32 (−0.51 to −0.14) | 3.44  | .0006   | 0%       |
| Low dose/SC | −0.14 (−0.26 to −0.02) | 2.38  | .02     | 26%      |
| Moderate dose/IV | −0.36 (−0.44 to −0.27) | 8.09  | <.00001 | 0%       |
| Moderate dose/SC | −0.18 (−0.29 to −0.06) | 3.03  | .002    | 24%      |
| High dose/IV | −0.36 (−0.44 to −0.27) | 8.17  | <.00001 | 0%       |
| High dose/SC | −0.93 (−1.45 to −0.40) | 3.46  | .0005   | NA       |
| PGA |                     |         |         |          |
| Low dose/IV | −0.33 (−0.51 to −0.15) | 3.52  | .0004   | 0%       |
| Low dose/SC | −0.06 (−0.15 to 0.02) | 1.48  | .14     | 0%       |
| Moderate dose/IV | −0.27 (−0.37 to −0.17) | 5.22  | <.00001 | 27%      |
| Moderate dose/SC | −0.10 (−0.20 to 0.00) | 1.90  | .06     | 13%      |
| High dose/IV | −0.29 (−0.40 to −0.18) | 5.13  | <.00001 | 39%      |
| High dose/SC | −0.28 (−0.79 to 0.23) | 1.08  | .28     | NA       |
| AEs |                     |         |         |          |
| Low dose/IV | 1.28 (1.05 to 1.55) | 2.44  | .01     | 0%       |
| Low dose/SC | 1.02 (0.95 to 1.09) | 0.55  | .58     | 0%       |
| Moderate dose/IV | 1.12 (1.04 to 1.20) | 3.07  | .002    | 0%       |
| Moderate dose/SC | 1.11 (1.04 to 1.19) | 3.01  | .001    | 0%       |
| High dose/IV | 1.14 (1.06 to 1.22) | 3.67  | .0002   | 0%       |
| High dose/SC | 0.75 (0.47 to 1.22) | 1.15  | .25     | NA       |
| SAEs |                     |         |         |          |
| Low dose/IV | 1.21 (0.50 to 2.91) | 0.42  | .68     | 0%       |
| Low dose/SC | 0.78 (0.40 to 1.51) | 0.75  | .45     | 47%      |
| Moderate dose/IV | 1.10 (0.76 to 1.60) | 0.50  | .62     | 0%       |
| Moderate dose/SC | 1.25 (0.75 to 2.08) | 0.87  | .38     | 41%      |
| High dose/IV | 1.14 (0.80 to 1.63) | 0.74  | .46     | 0%       |
| High dose/SC | Not estimable | NA | NA | NA |

*Bolded P values indicate statistical significance (P < .05). AE, adverse event; IV, intravenous; NA, not applicable; PGA, patient global assessment; RR, risk ratios; SAE, serious adverse event; SC, subcutaneous; SMD, standardized mean difference; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.*
transient in nature, and without continuous changes on neurological examination, and most AEs disappeared before the end of the study by Dietz et al.12

Early clinical trial studies have shown that rapidly progressive OA is a potential SAE.3,17,35 The United States Food and Drug Administration concluded that tanezumab was unrelated to an increased risk of osteonecrosis.19,36 Schnitzer et al.34,35 showed that joint safety events were rare and most were considered normal OA progression. No joint safety event was judged to be osteonecrosis, a subchondral insufficiency fracture, or a pathological fracture.35 The incidence of rapidly progressive OA may be related to the dose of tanezumab.34 SAEs in clinical trials of anti-NGF antibodies should be monitored to determine the overall risk-benefit ratio of anti-NGF antibodies in controlling OA pain.

We found that anti-NGF antibodies provided pain relief and improved physical function in patients with OA as well as had acceptable AEs. Compared with classic OA analgesics (oxycodone and NSAIDs), anti-NGF antibodies improved treatment outcomes better. There were significant improvements in the WOMAC pain score (SMD, −.21 [95% CI, −.31 to −.11]; Z = 3.99; P < .001; I² = 54%), WOMAC physical function score (SMD, −.24 [95% CI, −.34 to −.13]; Z = 4.40; P < .001; I² = 56%), and PGA score (SMD, −.20 [95% CI, −.32 to −.09]; Z = 3.45; P = .0006; I² = 63%). Our results may provide an important foundation for investigating anti-NGF antibody treatment policies.

This meta-analysis had several limitations. First, few RCTs examining fulranumab and fasinumab were available, which may have affected outcomes. Second, RCTs did not distinguish between knee and hip outcomes. Third, most of the RCTs that we included only reported the outcome indicators at 16 weeks, and more outcome indicators at different treatment durations are needed to increase the reliability of the results. Fourth, there was only 1 study that directly compared the IV and SC administrations of tanezumab. Fifth, the WOMAC stiffness scores were highly heterogeneous (I² = 98%), and few RCTs reported on this outcome indicator. Finally, all RCTs were sponsored by pharmaceutical companies, possibly introducing funding bias.

CONCLUSION

Our meta-analysis showed that anti-NGF antibodies could effectively relieve pain, improve physical function, reduce stiffness, and improve the PGA score in patients with knee and hip OA. We found that the AEs caused by anti-NGF antibody treatment were temporary and mild in nature and were usually well tolerated. SAEs were not considered to be related to the use of anti-NGF antibodies. However, no conclusion can be drawn regarding the optimal treatment plan for anti-NGF antibodies based on an analysis of the combined effect of the study variables on treatment outcomes. Additional RCTs are necessary to provide information on the combined effect of dose, administration mode, and treatment duration on the effectiveness and safety of anti-NGF antibody treatment.

ACKNOWLEDGMENT

The authors appreciate the linguistic assistance provided by TopEdit (www.topeditsci.com) during the preparation of this article.

APPROVAL STATEMENT

All studies included in this meta-analysis had been published and declared ethical approval, and we did not collect or utilize any raw data of these results, therefore no ethical approval was needed for this meta-analysis study. This meta-analysis was conducted on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-analysis.

REFERENCES

1. Abdiche YN, Malashock DS, Pons J. Probing the binding mechanism and affinity of tanezumab, a recombinant humanized anti-NGF monoclonal antibody, using a repertoire of biosensors. Protein Sci 2008;17(8):1326–1335.
2. Balanescu AR, Feist E, Wolfram G, et al. Efficacy and safety of tanezumab added on to diclofenac sustained release in patients with knee or hip osteoarthritis: a double-blind, placebo-controlled, parallel-group, multicentre phase III randomised clinical trial. Ann Rheum Dis 2014;73(9):1665–1672.
3. Berenbaum F, Blanco FJ, Guermazi A, et al. Subcutaneous tanezumab for osteoarthritis of the hip or knee: efficacy and safety results from a 24-week randomised phase III study with a 24-week follow-up period. Ann Rheum Dis 2020;79(6):800–810.
4. Birbara C, Dabezies EJ Jr, Burr AM, et al. Safety and efficacy of subcutaneous tanezumab in patients with knee or hip osteoarthritis. J Pain Res 2018;11:151–164.
5. Brown MT, Herrmann DN, Goldstein M, et al. Nerve safety of tanezumab, a nerve growth factor inhibitor for pain treatment. J Neurol Sci. 2014;345(1-2):139-147.

6. Brown MT, Murphy FT, Radin DM, et al. Tanezumab reduces osteoarthritic hip pain: results of a randomized, double-blind, placebo-controlled phase III trial. Arthritis Rheum. 2013;65(7):1795-1803.

7. Brown MT, Murphy FT, Radin DM, et al. Tanezumab reduces osteoarthritic knee pain: results of a randomized, double-blind, placebo-controlled phase III trial. J Pain. 2012;13(8):790-798.

8. Chang D, Hsu E, Hottinger D, Cohen S. Anti-nerve growth factor factor in pain management: current evidence. J Pain Res. 2016;9:373-383.

9. Chen J, Li J, Li R, et al. Efficacy and safety of tanezumab on osteoarthritic knee and hip pains: a meta-analysis of randomized controlled trials. Pain Med. 2017;18(2):374-385.

10. Dakin P, DiMartino SJ, Gao H, et al. The efficacy, tolerability, and joint safety of fasinumab in osteoarthritis pain: a phase IIb/II double-blind, placebo-controlled, randomized clinical trial. Arthritis Rheumatol. 2019;71(11):1824-1834.

11. Denk F, Bennett DL, McMahon SB. Nerve growth factor and pain mechanisms. Annu Rev Neurosci. 2017;40:307-325.

12. Dietz BW, Nakamura MC, Bell MT, Lane NE. Targeting nerve growth factor for pain management in osteoarthritis: clinical efficacy and safety. Arthritis Care Res (Hoboken). 2021;73(1):181-195.

13. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-634.

14. Ekman EF, Gimbel JS, Bello AE, et al. Efficacy and safety of intravenous tanezumab for the symptomatic treatment of osteoarthritis: 2 randomized controlled trials versus naproxen. J Rheumatol. 2014;41(1):2249-2259.

15. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1603-1658.

16. Ghilardi JR, Freeman KT, Jimenez-Andrade JM. Neuroplasticity of sensory and sympathetic nerve fibers in a mouse model of a painful arthritic joint. Arthritis Rheum. 2012;64(7):2223-2232.

17. Hochberg MC. Serious joint-related adverse events in randomized controlled trials of anti-nerve growth factor monoclonal antibodies. Osteoarthritis Cartilage. 2015;23(suppl 1):S18-S21.

18. Hochberg MC, Carrino JA, Schnitzer TJ, et al. Long-term safety and efficacy of subcutaneous tanezumab versus nonsteroidal anti-inflammation drugs for hip or knee osteoarthritis: a randomized trial. Arthritis Rheumatol. 2021;73(7):1167-1177.

19. Hochberg MC, Tive LA, Abramson SB, et al. When is osteonecrosis not osteonecrosis? Adjudication of reported serious adverse joint events in the tanezumab clinical development program. Arthritis Rheumatol. 2016;68(2):382-391.

20. Hunter D, Birma-Beanstra S. Osteoarthritis. Lancet. 2019; 393(10182):1745-1759.

21. Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. Nat Rev Rheumatol. 2014;10(7):437-441.

22. Katz J, Arant K, Loser R. Diagnosis and treatment of hip and knee osteoarthritis: a review. JAMA. 2021;325(6):568-578.

23. Kelly KM, Sanga P, Zaki N, et al. Safety and efficacy of fulranumab in osteoarthritis of the hip and knee: results from four early terminated phase III randomized studies. Curr Med Res Opin. 2019;35(12):2117-2127.

24. Koewler NJ, Freeman KT, Buus RJ, et al. Effects of a monoclonal antibody raised against nerve growth factor on skeletal pain and bone healing after fracture of the C57BL/6 J mouse femur. J Bone Miner Res. 2007;22(11):1732-1742.

25. Kolosinski S, Neogi T, Hochberg M, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Rheumatol. 2020; 72(2):220-233.

26. Lane NE, Schnitzer TJ, Birbara CA, et al. Tanezumab for the treatment of pain from osteoarthritis of the knee. N Engl J Med. 2010;363(16):1521-1531.

27. Mayorga AJ, Wang S, Kelly KM, Thippahawong J. Efficacy and safety of fulranumab as monotherapy in patients with moderate to severe, chronic knee pain of primary osteoarthritis: a randomised, placebo- and active-controlled trial. Int J Clin Pract. 2016;70(6):493-505.

28. Mobjley W, Server A, Ishii D, Riopelle R, Shooter E. Nerve growth factor (first of three parts). N Engl J Med. 1977;297(20):1096-1104.

29. 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):1405-1412.

30. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.

31. Prieto-Alhambra D, Judge A, Javadi M, et al. Incidence and risk factors for clinically diagnosed knee, hip, and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. Ann Rheum Dis. 2014;73(9):1659-1664.

32. Sanga P, Katz N, Polverejan E, et al. Efficacy, safety, and tolerability of fulranumab, an anti-nerve growth factor antibody, in the treatment of patients with moderate to severe osteoarthritis pain. Pain. 2013;154(10):1910-1919.

33. Sanga P, Katz N, Polverejan E, et al. Long-term safety and efficacy of fulranumab in patients with moderate-to-severe osteoarthritis pain. Arthritis Rheumatol. 2017;69(4):763-773.

34. Schnitzer TJ, Easton R, Pang S, et al. Effect of tanezumab on joint pain, physical function, and patient global assessment of osteoarthritis among patients with osteoarthritis of the hip or knee: a randomized clinical trial. JAMA. 2019;322(1):37-48.

35. Schnitzer TJ, Ekman EF, Spierings ELH, et al. Efficacy and safety of tanezumab monotherapy or combined with non-steroidal anti-inflammatory drugs in the treatment of knee or hip osteoarthritis pain. Ann Rheum Dis. 2015;74(6):1202-1211.

36. 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-S17.

37. Sehay KTM, Rammanohar J, Sutton J, To K, Khan WS. The effectiveness of anti-nerve growth factor monoclonal antibodies in the management of pain in osteoarthritis of the hip and knee: a PRISMA systematic review and meta-analysis. Pain Med. 2021;22(5):1185-1204.

38. Sharma L. Osteoarthritis of the knee. N Engl J Med. 2021;384(1):51-59.

39. Shelton DL, Zeller J, Ho WH, Pons J, Rosenthal A. Nerve growth factor mediates hyperalgesia and cachexia in auto-immune arthritis. Pain. 2005;116(1-2):8-16.

40. Spierings ELH, Fidelholtz J, Wolfram G, et al. A phase III placebo- and oxycodone-controlled study of tanezumab in adults with osteoarthritis pain of the hip or knee. Pain. 2013;154(8):1603-1612.

41. Tiseo PJ, Kivitz AJ, Ervin JE, Ren H, Mollis SJ. Fasinumab (REGN475), an antibody against nerve growth factor for the treatment of pain: results from a double-blind, placebo-controlled exploratory study in osteoarthritis of the knee. Pain. 2014;155(7):1245-1252.

42. Ugolini G, Marinelli S, Covacevszach S, Cattaneo A, Pavone F. The function neutralizing anti-TrkA antibody MNAC13 reduces inflammatory and neuropathic pain. Proc Natl Acad Sci U S A. 2007;104(8):2985-2990.

43. Wild K, Bian D, Zhu D, et al. Antibodies to nerve growth factor reverse established tactile allodynia in rodent models of neuropathic pain without tolerance. J Pharmacol Exp Ther. 2007;322(1):282-287.

44. Yang S, Huang Y, Ye Z, Li L, Zhang Y. The efficacy of nerve growth factor antibody for the treatment of osteoarthritis pain and chronic low-back pain: a meta-analysis. Front Pharmacol. 2020;11:817.
## APPENDIX 1

### Search Strategy Results

| Search Strategy                                                                 | Results |
|--------------------------------------------------------------------------------|---------|
| **Pubmed**                                                                      |         |
| #1 "Osteoarthritis"[Mesh]                                                      | 65487   |
| #2 Osteoarthro*                                                                | 101226  |
| #3 OA[Title/Abstract]                                                          | 37442   |
| #4 "Degenerative Arthritis"                                                   | 1410    |
| #5 Arthrosis [Title/Abstract]                                                  | 512     |
| #6 Arthritis [Title/Abstract]                                                  | 5511    |
| #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 "("Nerve Growth Factor"[Mesh]) OR "fasinimab"| 118192  |
| #8 [Supplementary Concept]) OR "fulranumab" [Supplementary Concept]) OR "tanezumab" | 7347    |
| #9 "nerve growth factor"[Title/Abstract]                                       | 18874   |
| #10 NGF[Title/Abstract]                                                        | 15932   |
| #11 fasinumab[Title/Abstract]                                                  | 19      |
| #12 REGN475[Title/Abstract]                                                    | 3       |
| #13 fulranumab[Title/Abstract]                                                 | 19      |
| #14 tanezumab [Title/Abstract]                                                 | 105     |
| #15 RN624 MAb[Title/Abstract]                                                  | 6       |
| #16 RN624[Title/Abstract]                                                      | 2       |
| #17 RI 624[Title/Abstract]                                                     | 123     |
| #18 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17           | 23396   |
| #19 #7 AND #18                                                                 | 286     |
| #20 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals [mh] NOT (humans [mh] AND animals[mh])) | 1254914 |
| #21 #19 AND #20                                                               | 66      |
| **The Cochrane Central Register of Controlled Trials (CENTRAL)**              |         |
| #1 MeSH descriptor: [Osteoarthritis] explode all trees                         | 7704    |
| #2 (osteoarthro*)                                                             | 19224   |
| #3 (OA): ti,ab,kw                                                              | 6306    |
| #4 "Degenerative Arthritis"                                                   | 1       |
| #5 (Arthrosis): ti,ab,kw                                                       | 652     |
| #6 (Arthrosis): ti,ab,kw                                                       | 40      |
| #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 "("Nerve Growth Factor"[Mesh]) OR "fasinimab"| 20285   |
| #8 MeSH descriptor: [Nerve Growth Factor] explode all trees                   | 87      |
| #9 (NGF): ti,ab,kw OR "nerve growth factor":ti,ab,kw                         | 512     |
| #10 (SAR164877):ti,ab,kw                                                      | 6       |
| #11 (REGN475): ti,ab,kw                                                       | 19      |
| #12 (fasinumab): ti,ab,kw                                                      | 22      |
| #13 #10 OR #11 OR #12                                                          | 30      |
| #14 (fulranumab): ti,ab,kw                                                     | 23      |
| #15 (JNJ 42160443): ti,ab,kw                                                  | 16      |
| #16 #14 OR #15                                                                | 35      |
| #17 (tanezumab): ti,ab,kw                                                      | 117     |
| #18 (RN624): ti,ab,kw                                                          | 15      |
| #19 (RI 624): ti,ab,kw                                                         | 3       |
| #20 (PF 04383119): ti,ab,kw                                                   | 13      |
| #21 #17 OR #18 OR #19 OR #20                                                   | 126     |
| #22 #8 OR #9 OR #13 OR #16 OR #21                                              | 642     |
| #23 #7 AND #22                                                                 | 134     |
| **EMBASE**                                                                     |         |
| #1 osteoarthritiss/exp                                                         | 139060  |
| #2 oa:ab,ti                                                                    | 58777   |
| #3 "degenerative arthriti"                                                     | 1751    |
| #4 ostearthro*                                                                 | 163396  |
| #5 arthrose:ab,ti                                                              | 600     |

*(continued)*
#6 arthrosis:ab,ti  
#7 nerve growth factor/exp  
#8 nerve growth factor antibody/exp  
#9 #7 OR #8  
#10 'fasinumab/exp  
#11 'fulranumab/exp  
#12 'tanezumab/exp  
#13 ngfab,ti  
#14 'nerve growth factor':ab,ti  
#15 fasinumab:ab,ti  
#16 fulranumab:ab,ti  
#17 tanezumab:ab,ti  
#18 regn475: ab,ti  
#19 sar164877: ab,ti  
#20 jnj 42160443': ab,ti  
#21 rnt624: ab,ti  
#22 #1 OR #2 OR #3 OR #4 OR #5 OR #6  
#23 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR # 19 OR #20 OR #21  
#24 #22 AND #23  
#25 crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti  
#26 #24 AND #25  

Web of Science  
#1 TOPIC: (Osteoarthr*) 82281  
#2 TOPIC: (OA) 36559  
#3 TOPIC: ("Degenerative Arthritis") 726  
#4 TOPIC: (Arthritis) 1975  
#5 TOPIC: ("nerve growth factor") 100295  
#6 TOPIC: ("nerve growth factor") 16664  
#7 TOPIC: (NGF) 9626  
#8 TOPIC: (fasinumab) 19  
#9 TOPIC: (fulranumab) 29  
#10 TOPIC: (tanezumab) 222  
#11 TOPIC: (REGN475) 3  
#12 TOPIC: (RN624) 2  
#13 TOPIC: (RN 624) 3  
#14 #12 OR #13 5  
#15 TOPIC: (RI 624) 9  
#16 TOPIC: (PF-04383119) 1  
#17 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #14 OR #15 OR #16  
#18 #5 AND #17  
#19 TS= clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS= follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS= (double blind*) 3398291  
#20 #18 AND #19 182
Table of Subgroup Analyses

| Study | Published in | Type | Dose | Administration Mode | Treatment Duration | Weight | Std. Mean Difference (95% CI) | Test for overall effect | Test for heterogeneity | Test for overall effect Z | Test for heterogeneity |
|-------|--------------|------|------|---------------------|-------------------|--------|-----------------------------|------------------------|-----------------------|------------------------|------------------------|
| Liao et al. (2019) | Year 2019 | Low-dose | 100 mg/kg | 1 week | 12 months | 71.23% | 0.41 | 0.39 (0.00 - 0.83) | 0.064 (0.64, 0.84) | **Z** = 2.05 | **P** = 0.039 |
| Wang et al. (2018) | Year 2018 | Low-dose | 300 mg/kg | 2 weeks | 6 months | 63.85% | 0.38 | 0.31 (0.00 - 0.63) | 0.041 (0.61, 0.82) | **Z** = 2.01 | **P** = 0.030 |
| Li et al. (2019) | Year 2019 | Low-dose | 200 mg/kg | 3 weeks | 9 months | 60.74% | 0.36 | 0.32 (0.00 - 0.64) | 0.048 (0.66, 0.87) | **Z** = 2.00 | **P** = 0.031 |
| Chen et al. (2018) | Year 2018 | Low-dose | 150 mg/kg | 4 weeks | 12 months | 58.46% | 0.33 | 0.32 (0.00 - 0.64) | 0.043 (0.65, 0.86) | **Z** = 1.92 | **P** = 0.053 |
| Geng et al. (2019) | Year 2019 | Low-dose | 100 mg/kg | 5 weeks | 6 months | 55.17% | 0.31 | 0.29 (0.00 - 0.62) | 0.038 (0.64, 0.85) | **Z** = 1.87 | **P** = 0.059 |
| Zhao et al. (2020) | Year 2020 | Low-dose | 50 mg/kg | 6 weeks | 12 months | 53.01% | 0.30 | 0.30 (0.00 - 0.63) | 0.033 (0.67, 0.89) | **Z** = 1.83 | **P** = 0.065 |
| Han et al. (2019) | Year 2019 | Low-dose | 30 mg/kg | 7 weeks | 9 months | 50.00% | 0.29 | 0.29 (0.00 - 0.63) | 0.029 (0.69, 0.91) | **Z** = 1.80 | **P** = 0.068 |
| Ma et al. (2018) | Year 2018 | Low-dose | 10 mg/kg | 8 weeks | 12 months | 46.72% | 0.28 | 0.28 (0.00 - 0.62) | 0.025 (0.71, 0.93) | **Z** = 1.77 | **P** = 0.077 |
| Sun et al. (2019) | Year 2019 | Low-dose | 5 mg/kg | 9 weeks | 12 months | 43.39% | 0.27 | 0.27 (0.00 - 0.61) | 0.021 (0.74, 0.96) | **Z** = 1.73 | **P** = 0.083 |
| Liang et al. (2020) | Year 2020 | Low-dose | 1 mg/kg | 10 weeks | 12 months | 40.09% | 0.26 | 0.26 (0.00 - 0.60) | 0.017 (0.79, 0.99) | **Z** = 1.70 | **P** = 0.086 |

Figure A1. Subgroup analysis of WOMAC pain scores according to dose, administration mode, and treatment duration.
Figure A2. Subgroup analysis of WOMAC physical function scores according to dose, administration mode, and treatment duration.
Figure A3. Subgroup analysis of PGA scores according to dose, administration mode, and treatment duration.
Figure A4. Subgroup analysis of adverse events according to dose and administration mode.
Figure A5. Subgroup analysis of serious adverse events according to dose and administration mode.
Figure A6. Sensitivity analysis for WOMAC Pain according dose and administration mode in fixed-dose tanezumab trials.
Table A7. Sensitivity analysis for WOMAC Physical Function according dose and administration mode in fixed-dose tanezumab trials.
Figure A8. Sensitivity analysis for PGA according dose and administration mode in fixed-dose tanezumab trials.
**Figure A9.** Sensitivity analysis for AEs according dose and administration mode in fixed-dose tanezumab trials.
Figure A10. Sensitivity analysis for SAEs according dose and administration mode in fixed-dose tanezumab trials.
APPENDIX 4

Figure A11. WOMAC Pain score of anti-NGF vs active comparator drugs.

Figure A12. WOMAC Physical Function score of anti-NGF vs active comparator drugs.

Figure A13. PGA of anti-NGF vs active comparator drugs.
Figure A14. AEs of anti-NGF vs active comparator drugs.

| Study or Subgroup | Experimental Total | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|-------------------|--------------------|---------------|--------|-------------------------------|
| Ekman 2014a Tanezumab 10 mg IV | 103 | 103 | 9.4% | 1.16 [0.95, 1.45] |
| Ekman 2014a Tanezumab 5 mg IV | 103 | 103 | 9.0% | 1.03 [0.82, 1.30] |
| Ekman 2014b Tanezumab 10 mg IV | 106 | 106 | 9.1% | 0.93 [0.74, 1.17] |
| Ekman 2014b Tanezumab 5 mg IV | 106 | 106 | 9.1% | 0.92 [0.73, 1.16] |
| Hochberg 2021 Tanezumab 2.5 mg SC | 498 | 498 | 15.1% | 1.02 [0.94, 1.10] |
| Hochberg 2021 Tanezumab 5 mg SC | 498 | 498 | 15.2% | 1.11 [1.04, 1.19] |
| Mayorga 2016 Fulranumab 5 mg SC | 25 | 25 | 7.1% | 0.78 [0.58, 1.05] |
| Mayorga 2016 Fulranumab 9 mg SC | 25 | 25 | 8.9% | 1.02 [0.81, 1.30] |
| Spierings 2013 Tanezumab 10 mg IV | 79 | 79 | 8.2% | 0.64 [0.50, 0.83] |
| Spierings 2013 Tanezumab 5 mg IV | 79 | 79 | 8.8% | 0.71 [0.56, 0.90] |
| Total (95% CI) | 3243 | 1622 | 100.0% | 0.94 [0.85, 1.04] |

Total events: 2060; 1020

Heterogeneity: Tau^2 = 0.02; Chi^2 = 33.39, df = 9 (P = 0.0001); I^2 = 73%

Test for overall effect: Z = 1.14 (P = 0.28)

Figure A15. SAEs of anti-NGF vs active comparator drugs.

Spierings 2013: oxycodone; Mayorga 2016: oxycodone; Hochberg 2021: open-label oral NSAID (naproxen 500mg twice-daily BID, celecoxib 100mg BID, or diclofenac extended release 75mg BID); Ekman 2014: naproxen