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Does anti-nerve growth factor monoclonal antibody treatment have the potential to replace nonsteroidal anti-inflammatory drugs and opioids in treating hip or knee osteoarthritis? A systematic review of randomized controlled trials

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- *Purpose:* Considering the adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids for treating osteoarthritis (OA), development of drugs that are more effective and better tolerated than existing treatments is urgently needed. This systematic review aimed to evaluate the efficacy and safety of anti-nerve growth factor (NGF) monoclonal antibodies vs active comparator therapy, such as NSAIDs and oxycodone, in treating hip or knee OA.
- *Methods:* Databases were comprehensively searched for randomized controlled trials (RCTs) published before January 2022. Efficacy and safety outcomes were assessed.
- *Results:* Six RCTs that included 4325 patients were identified. Almost all the RCTs indicated that moderate doses of anti-NGF monoclonal antibody treatment significantly improved efficacy outcomes based on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score, the WOMAC physical function score and the Patient's Global Assessment compared with those of the active comparator. At least half of the RCTs indicated that the incidence of severe adverse events, withdrawals due to adverse events (AEs) and total joint replacement were not significantly different between anti-NGF monoclonal antibody treatment and active comparator therapy, but the outcomes of some studies may have been limited by a short duration of follow-up. Most RCTs suggested that anti-NGF monoclonal antibody treatment had a lower incidence of gastrointestinal and cardiovascular AEs. However, the majority of RCTs reported a higher incidence of abnormal peripheral sensation with anti-NGF monoclonal antibody treatment. Furthermore, the higher incidence of rapidly progressive osteoarthritis (RPOA) with anti-NGF monoclonal antibody treatment should also not be overlooked, and the identification of patient characteristics that increase the risk of RPOA is critical in further studies.
- *Conclusion:* Based on the current research evidence, anti-NGF monoclonal antibodies are not yet a replacement for analgesic drugs such as NSAIDs but might be a new treatment option for hip or knee OA patients who are intolerant or unresponsive to nonopioid or opioid treatment. Notably, however, considering the inconsistency and inconclusive evidence on the safety outcomes of recent studies, more research is needed, and long-term follow-up is required.

Keywords

- anti-NGF monoclonal antibody
- osteoarthritis
- OA
- randomized controlled trials
- systematic review

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Introduction

Osteoarthritis (OA) is a severe and painful joint disease that limits daily activities and reduces quality of life. OA is estimated to be the third leading cause of disability, affecting approximately 350 million people worldwide (1, 2). Especially for patients with moderate to severe OA, the effective management of chronic pain associated with OA is a major concern for clinicians. Although nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids are currently the dominant analgesic therapy for OA, the lack of pain relief and intolerable side effects of these analgesics have limited their use to some extent (3, 4). Therefore, there is an urgent need to develop drugs that are more effective and better tolerated by patients than existing treatments.

Nerve growth factor (NGF) is a neurotrophic factor associated with pain signal transduction and nociceptor receptor gene expression (5). It is a nociceptor sensitizer and has been studied as a potential alternative target for the treatment of pain in OA. After tissue injury or inflammation, NGF is released and binds to tropomyosin receptor kinase (Trk) A, which can lead to central sensitization (5), induce the expression of peripheral and central pain-related substances and make adjacent pain-sensing neurons sensitive to inflammation, thereby mediating pain (6, 7, 8). The expression of NGF is significantly increased at the site of trauma and inflammation (9). In addition, NGF levels in synovial fluid have been reported to be significantly higher in patients with OA than in normal subjects (10), so NGF is also considered to be an important pathogenic factor or a pathological product involved in the pain process. Inhibition of NGF binding to its receptor can downregulate NGF expression, thus alleviating pain, improving limb function and relieving OA symptoms.

The efficacy and safety of anti-NGF monoclonal antibodies vs placebo in the treatment of OA have been reported in systematic reviews, and the curative effect of anti-NGF monoclonal antibodies has been affirmed. However, a systematic review of the efficacy and safety of anti-NGF monoclonal antibodies compared to those of analgesic drugs such as NSAIDs and oxycodone is lacking. Whether anti-NGF monoclonal antibodies are superior to analgesic drugs is unknown. In addition, given the safety issue (11, 12), the Food and Drug Administration (FDA) has mandated that anti-NGF monoclonal antibodies and NSAIDs should not be used in combination and has called for more research on anti-NGF monoclonal antibodies at lower doses. Therefore, the purpose of this study is to systematically review whether lower doses of anti-NGF monoclonal antibodies might have the potential to replace analgesic drugs such as NSAIDs and oxycodone as another effective option for the treatment of OA.

Methods

The systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (13, 14).

Search strategy and selection criteria

A comprehensive search was conducted through PubMed, Embase, the Cochrane Library and Web of Science. The keywords used were 'nerve growth factor antibody', 'anti-NGF', 'anti-nerve growth factor monoclonal antibody', 'tanezumab', 'fulranumab', 'fasinumab' and 'osteoarthritis.' Studies published from the inception of the database to January 2022 were retrieved. The references of the articles included were also searched. Each article was manually cross-checked. When there was a disagreement, a consensus was reached through negotiation.

Eligibility criteria

The inclusion criteria were as follows: (1) studies in which the participants were adult patients diagnosed with hip or knee OA according to the American College of Rheumatology criteria with radiographic confirmation (Kellgren–Lawrence grade $\geq$ 2 on a scale of 0–4); (2) studies in which the experimental group was treated with anti-NGF MAB treatment and the control group was treated with an active comparator; (3) studies that included information on the Western Ontario and McMaster Universities Osteoarthritis Index (WOAMC) pain score (scale of 0–10), WOMAC physical function score (scale of 0–10), patient's global assessment (PGA) (5-point Likert scale), number of withdrawals due to adverse events (AEs), severe adverse events (SAEs), abnormal peripheral sensation, rapidly progressive OA (RPOA), total joint replacement (TJR) and cardiovascular and gastrointestinal events and (4) studies that had a randomized controlled trial (RCT) design.

The exclusion criteria were as follows: (1) the experimental group was treated with anti-NGF MAB in combination with other active treatments; (2) the control group received only placebo and no other active treatments and (3) studies with incomplete data.

Data extraction

Two researchers independently extracted the data, which included the first author, year of publication, type and dose of intervention, trial size, patient sex, age, outcome measures and duration of follow-up. Disagreements were resolved through discussion, and, if necessary, a third investigator would make the final decision.

Risk of bias assessment

The methodological quality included in the study was assessed by two reviewers with the Cochrane Collaboration risk of bias assessment tool (15), which evaluates the following domains: random sequence generation, allocation concealment, blinding of the participants and outcome assessors, incomplete outcome data, selective reporting and other bias. Each component was considered to have a low, unclear or high risk of bias.

Statistical analysis

Reviewer Manager (v 5.4; Cochrane Collaboration) was used to create forest plots. The mean baseline-to-end point changes and their S.D. were obtained. For the efficacy outcomes, the weighted mean difference and 95% CIs were reported. For the safety outcomes, data were reported as frequencies with percentages, and the relative risk (RR) values for the studies were also reported with their 95% CIs. If only the S.E. was reported, the S.D. was calculated based on the reported S.E. and sample size. When the mean, S.E. or S.D. were not provided in an article, we extracted the values from charts or graphs, as needed. Subgroup analysis for different types of active treatments was performed. A P value <0.05 indicated a significant difference.

Results

Selection of the included studies

A total of 397 studies were retrieved through the literature search. Thirty-six studies remained after the titles and abstracts were screened. Then, the full texts were read. Five studies were finally selected according to the inclusion and exclusion criteria (see Supplementary Fig. 1 for details, see section on supplementary materials given at the end of this article).

Characteristics of the included studies

A total of 6 RCTs, including 4325 patients, were included in the analysis. One of the studies involved two RCTs (16). Interventions were subcutaneous administration in two studies (17, 18), while the other interventions were intravenous administration (16, 19, 20). Two studies had a follow-up of more than 48 weeks (safety outcomes). The characteristics of the included clinical trials are summarized in Table 1. Among the included studies, tanezumab doses of 2.5, 5 and 10 mg were reported. Fulranumab doses of 3 and 9 mg were reported. Tanezumab 2.5 mg was assigned to the low-dose group, tanezumab 5 mg and fulranumab 3 mg were assigned to the medium-dose group and tanezumab 10 mg and fulranumab 9 mg were assigned to the high-dose group. Given the safety concerns, we included only the low- to medium-dose group; however, only one study included a low dose of anti-NGF monoclonal antibodies (tanezumab 2.5 mg) (18), so we compared only the medium dose of anti-NGF monoclonal antibodies with the active comparator group to maintain as much consistency in the study as possible. In the active comparator group, four RCTs used NSAIDs (16, 18, 19) and two RCTs used oxycodone controlled release (CR) (17, 20). We conducted subgroup analysis according to different types of active control groups.

Risk of bias assessment

The quality of all the studies was relatively high. Although all the studies were RCTs, two studies (16, 20) did not report the generation of the random sequence. Two studies (16, 20) did not clearly indicate whether the outcome assessors and participants were blinded, so the risk of bias for this domain was judged as unclear. The methodological quality of the included studies is presented in Supplementary Figs. 2 and 3.

Efficacy

WOMAC pain score

A total of 6 RCTs (16, 17, 18, 19, 20) involving 4295 patients reported WOMAC pain scores. All the studies showed that anti-NGF MAB treatment exhibited significantly greater pain relief than the active comparator did ($P < 0.05$) (Fig. 1A). Similarly, in the subgroup analysis, anti-NGF MAB treatment was also superior to NSAIDs (Fig. 1B) and oxycodone CR (Fig. 1C) in improving WOMAC pain scores ($P < 0.05$).

WOMAC physical score

A total of 6 RCTs (16, 17, 18, 19, 20) involving 4295 patients reported WOMAC physical scores. All the studies showed that anti-NGF monoclonal antibody treatment resulted in greater improvements in the WOMAC physical score than did the active comparator ($P < 0.05$) (Fig. 2A). Similarly, in the subgroup analysis, anti-NGF monoclonal antibody treatment was superior to NSAIDs in improving WOMAC physical scores ($P < 0.05$) (Fig. 2B) and was superior to oxycodone CR ($P<0.05$) (Fig. 2C).

PGA

A total of 6 RCTs (16, 17, 18, 19, 20) involving 4295 patients reported PGA results. Four of six RCTs (16, 17, 20) reported that the estimate of PGA demonstrated significant differences in favour of anti-NGF monoclonal antibody treatment ($P < 0.05$), with the remaining two studies reporting no significant differences between groups (Fig. 3A). In the subgroup analysis, two of four RCTs (16) reported that anti-NGF monoclonal antibody treatment was superior to NSAIDs in improving *PGA* scores ($P<0.05$) (Fig. 3B), and all the RCTs (17, 20) showed that anti-NGF monoclonal antibody treatment was superior to oxycodone CR ($P<0.05$) (Fig. 3C).

Table 1 Characteristics of the included studies.[a]

Reference	Interventions	No. of subjects (% females)	Mean age (years)	Method of administration	Efficacy outcomes		Safety outcomes	
					Outcome	Endpoint	Outcome	Endpoint
Hochberg *et al.* (18)	Tanezumab 5 mg, naproxen 500 mg, or celecoxib 100 mg, or diclofenac 75 mg bid	1994 (66.0%)	60.8	s.c. Q8wk	WOMAC pain, WOMAC physical function, PGA	16 weeks	Withdrawals due to AEs, SAEs, RPOA, TJR, abnormal peripheral sensation	80 weeks
Mayorga *et al.* (17)	Fulranumab 3 mg, Oxycodone CR 10–20 mg bid	98 (56.1%)	59.9	s.c. Q4wk	WOMAC pain, WOMAC physical function, PGA	16 weeks	Withdrawals due to AEs, SAEs, TJR, abnormal peripheral sensation, cardiovascular and gastrointestinal events	16 weeks
Ekman *et al.* (16)	Tanezumab 5 mg, naproxen 500 mg bid	412 (61.0%)	61.3	i.v. Q8wk	WOMAC pain, WOMAC physical function, PGA	16 weeks	Withdrawals due to AEs, SAEs, abnormal peripheral sensation, cardiovascular and gastrointestinal events	24 weeks
Ekman *et al.* (16)	Tanezumab 5 mg, placebo, naproxen 500 mg bid	422 (64.0%)	60.1	i.v. Q8wk	WOMAC pain, WOMAC physical function, PGA	16 weeks	Withdrawals due to AEs, SAEs, abnormal peripheral sensation, cardiovascular and gastrointestinal events	24 weeks
Spierings *et al.* (20)	Tanezumab 5 mg, Oxycodone 10–40mg q12h	319 (61.1%)	57.7	i.v. Q8wk	WOMAC pain, WOMAC physical function, PGA	8 weeks	Withdrawals due to AEs, SAEs, abnormal peripheral sensation, cardiovascular and gastrointestinal events	16 weeks
Schnitzer *et al.* (19)	Tanezumab 5 mg, naproxen 500 mg or celecoxib 100 mg bid	1080 (72.2%)	61.6	i.v. Q8wk	WOMAC pain, WOMAC physical function	16 weeks	Withdrawals due to AEs, SAEs, RPOA, TJR, abnormal peripheral sensation	64 weeks

AEs, adverse events; PGA, patient's global assessment; RPOA, Rapidly progressive OA; SAEs, serious adverse events; TJR, total joint replacement.; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Safety

Withdrawals due to adverse events

A total of 6 RCTs (16, 17, 18, 19, 20) involving 4325 patients reported withdrawals due to AEs. The risk of withdrawals due to AEs at final follow-up ranged from 1.2% to 14.6% for anti-NGF monoclonal antibody treatment and from 5.2% to 16.0% for the active comparator (8.3% vs 7.1% overall). One RCT (16) showed that the incidence of withdrawals due to AEs was significantly lower in the anti-NGF monoclonal antibody treatment group than in the NSAID group (1.9% vs 7.6%, RR: 0.25, $P < 0.05$). However, one RCT (18) indicated that the incidence of withdrawals due to AEs was significantly higher in the anti-NGF monoclonal antibody treatment group than in the NSAID group (8.8% vs 5.2%, RR: 1.69, $P < 0.05$). The remaining two RCTs (16, 19) did not report significant differences between groups. In addition, one RCT (20) demonstrated that the incidence of withdrawals due to AEs was significantly lower in the anti-NGF monoclonal antibody treatment group than in the oxycodone CR group (1.2% vs 10.1%, RR: 0.12, $P < 0.05$). However, the remaining RCT (17) showed that there was no significant difference between the two groups. The safety outcomes of individual studies are summarized in Table 2.

Severe adverse events

A total of 6 RCTs (16, 17, 18, 19, 20) involving 4325 patients reported SAE results. The risk of SAEs at final follow-up ranged from 0% to 11.0% for anti-NGF monoclonal antibody treatment and from 2.4% to 8.0% for the active comparator (7.8% vs 6.0% overall). One (18) RCT indicated that the incidence of SAEs was significantly higher in the anti-NGF monoclonal antibody treatment group than in the NSAID group (11.0% vs 6.6%, RR: 1.66, $P<0.05$). However, the remaining three RCTs (16, 19) did not report significant differences between groups. In addition, two RCTs (17, 20) showed that there was no significant difference between the anti-NGF monoclonal antibody treatment and oxycodone CR groups.

Rapidly progressive OA

A total of two RCTs (18, 19) involving 3074 patients reported RPOA results. The risk of RPOA at final follow-up ranged from 0.7% to 6.3% for anti-NGF monoclonal antibody treatment and from 0.2% to 1.2% for the active comparator (4.4% vs 0.8% overall). One RCT (18) demonstrated that the incidence of RPOA was significantly higher in the anti-NGF monoclonal antibody treatment group than in the NSAID group (6.3% vs 1.2%, RR 5.24, $P < 0.05$). The other RCT (17) reported that the differences between the two groups did not reach statistical significance.

Total joint replacement

A total of 5 RCTs (16, 17, 18, 19) involving 3908 patients reported TJR results. The risk of TJR at final follow-up ranged from 0% to 8.0% for anti-NGF monoclonal antibody treatment and from 0% to 4.7% for the active comparator (5.2% vs 2.6% overall). One of four RCTs (18) demonstrated that the incidence of TJR was significantly

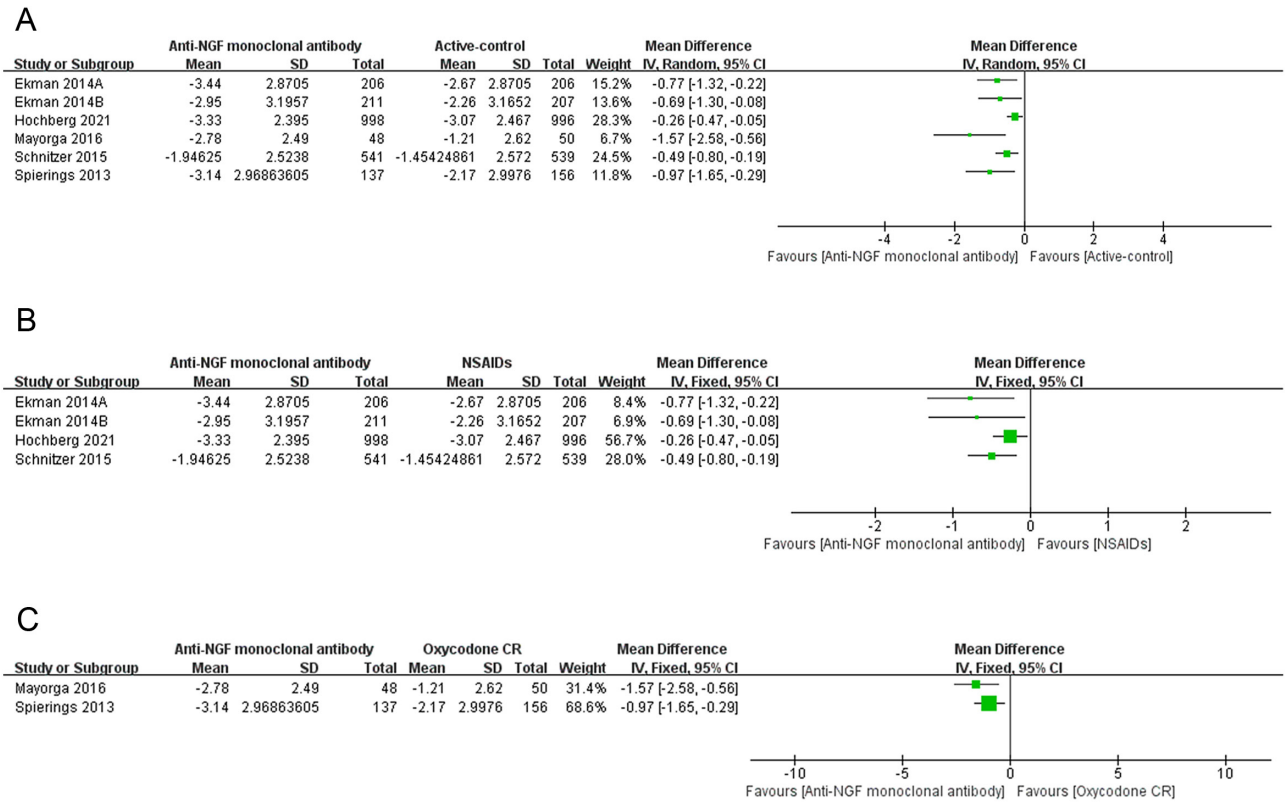

Figure 1

Forest plot of WOMAC pain scores detailing mean differences and 95% CIs comparing anti-NGF monoclonal antibody treatment with active control (A), mean differences and 95% CIs comparing anti-NGF monoclonal antibody treatment with NSAIDs (B), mean differences and 95% CIs comparing anti-NGF monoclonal antibody treatment with oxycodone CR (C). CR, controlled release; IV, inverse variance; NSAIDs, nonsteroidal anti-inflammatory drugs; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

higher in the anti-NGF monoclonal antibody treatment group than in the NSAID group (8.0% vs 2.6%, RR: 3.07, $P < 0.05$), with the remaining three RCTs (16, 19) not reporting significant differences between groups. In addition, one RCT (17) showed that there was no significant difference between the anti-NGF monoclonal antibody treatment and oxycodone CR groups.

Abnormal peripheral sensation

A total of 6 RCTs (16, 17, 18, 19, 20) involving 4325 patients reported abnormal peripheral sensation results. The risk of abnormal peripheral sensation at final follow-up ranged from 3.2% to 11.7% for anti-NGF monoclonal antibody treatment and from 1.4% to 16.0% for the active comparator (7.2% vs 3.8% overall). Three of four RCTs (16, 18, 19) showed that the incidence of abnormal peripheral sensation was significantly higher in the anti-NGF monoclonal antibody treatment group than in the NSAID group (10.9% vs 4.3%, RR: 2.56, $P< 0.05$; 3.2% vs 1.4%, RR: 2.28, $P< 0.05$; 10.7% vs 5.8%, RR: 1.86, $P< 0.05$, respectively), with the remaining RCT (16) reporting no significant differences between groups. In addition, one RCT (20) demonstrated that the incidence of abnormal peripheral sensation was significantly higher in the anti-NGF monoclonal antibody treatment group than in the oxycodone CR group (8.1% vs 2.5%, RR: 3.19, $P < 0.05$). Another RCT (17) reported that there was no significant difference between the two groups.

Cardiovascular and gastrointestinal events

A total of 6 RCTs (16, 17, 18, 19, 20) involving 4325 patients reported cardiovascular and gastrointestinal event results. The risk of cardiovascular and gastrointestinal events at final follow-up ranged from 0.4% to 22.9% for anti-NGF monoclonal antibody treatment and from 1.0% to 62.0% for the active comparator (2.8% vs 8.0% overall). Two of four RCTs (16) showed that the incidence of cardiovascular and gastrointestinal events was significantly lower in the anti-NGF monoclonal antibody treatment group than in the NSAID group (1.5% vs 5.3%, RR: 0.27, $P<0.05$; 2.4% vs 7.6%, RR: 0.31, $P< 0.05$, respectively), with the remaining two RCTs (18, 19) reporting that the differences between

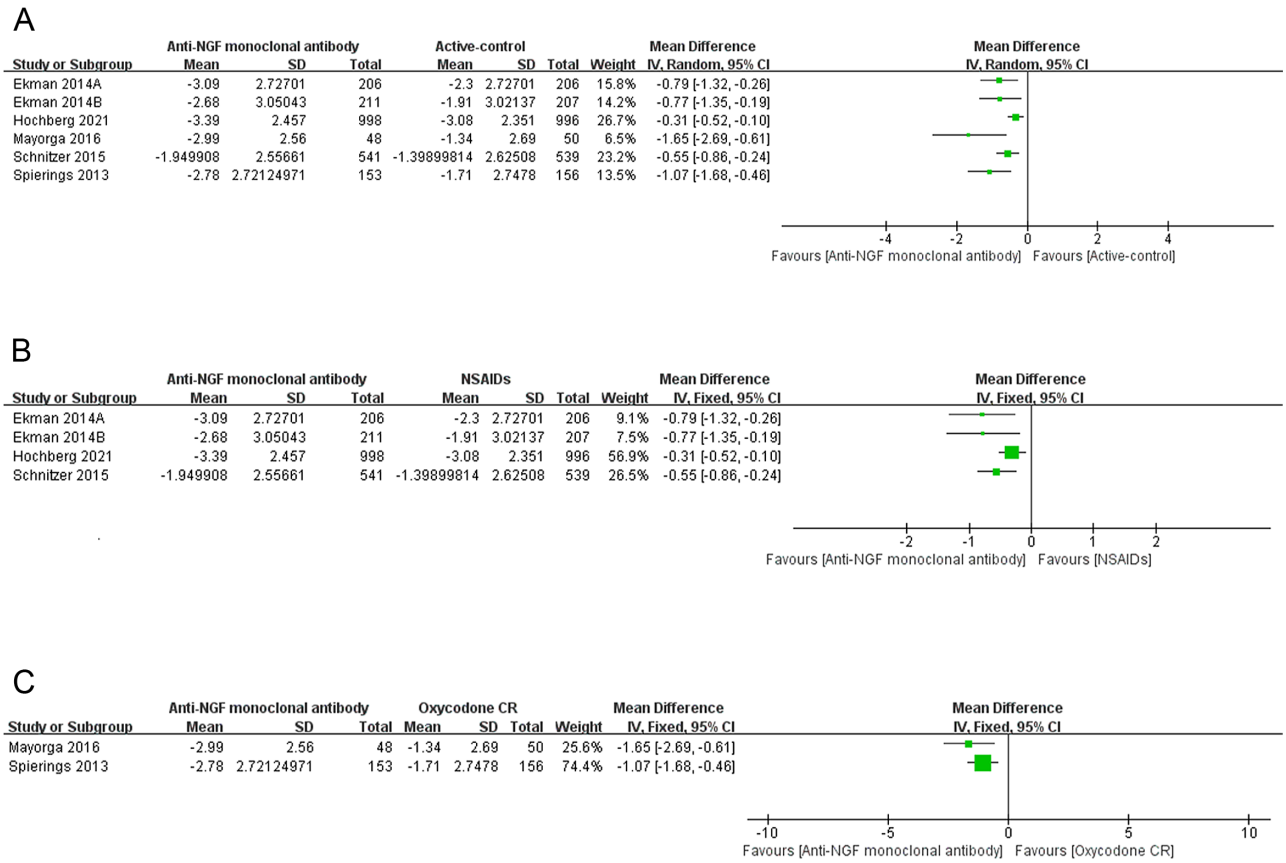

Figure 2

Forest plot of WOMAC physical function scores detailing mean differences and 95% CIs comparing anti-NGF monoclonal antibody treatment with active control (A), mean differences and 95% CIs comparing anti-NGF monoclonal antibody treatment with NSAIDs (B), mean differences and 95% CIs comparing anti-NGF monoclonal antibody treatment with oxycodone CR (C). CR, controlled release; IV, inverse variance; NSAIDs, nonsteroidal anti-inflammatory drugs; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

the two groups did not reach statistical significance. In addition, both RCTs (17, 20) indicated that the incidence of cardiovascular disease and gastrointestinal disease was significantly lower in the anti-NGF monoclonal antibody treatment group than in the oxycodone CR group (22.9% vs 62.0%, RR: 0.37, $P< 0.05$; 6.8% vs 43.7%, RR: 0.16, $P< 0.05$, respectively).

Discussion

This systematic review provides an overview of the efficacy and safety of anti-NGF monoclonal antibody treatment vs an active comparator. The gathered findings suggested that compared with NSAIDs and oxycodone CR, anti-NGF monoclonal antibody treatment showed a statistically significant improvement in the WOMAC pain score, WOMAC physical score and PGA in moderate to severe hip or knee OA. The safety of anti-NGF monoclonal antibody treatment vs NSAIDs and oxycodone CR in the treatment of hip or knee OA has been evaluated from several aspects, but there are conflicting results in the current literature. One long-term RCT (18) indicated that the incidence of withdrawal due to AEs, SAEs, RPOA, TJR and abnormal peripheral sensation was significantly higher in the anti-NGF monoclonal antibody treatment group than in the NSAID group. In contrast, another long-term RCT (19) suggested that there was no significant difference in withdrawal due to AEs, SAEs, RPOA and TJR between the anti-NGF monoclonal antibody treatment and NSAID groups except for abnormal peripheral sensation. However, this study was impacted by a clinical hold. Most of the remaining RCTs did not show a significant difference in withdrawal due to AEs, SAEs and TJR between groups, and two RCTs (16, 20) showed a lower incidence of withdrawal due to AEs with anti-NGF monoclonal antibody treatment. More than half of the RCTs reported a higher incidence of abnormal peripheral sensation with anti-NGF monoclonal antibody treatment but a lower incidence of cardiovascular and gastrointestinal events. One of the included RCTs (18) reported that anti-NGF monoclonal antibody treatment

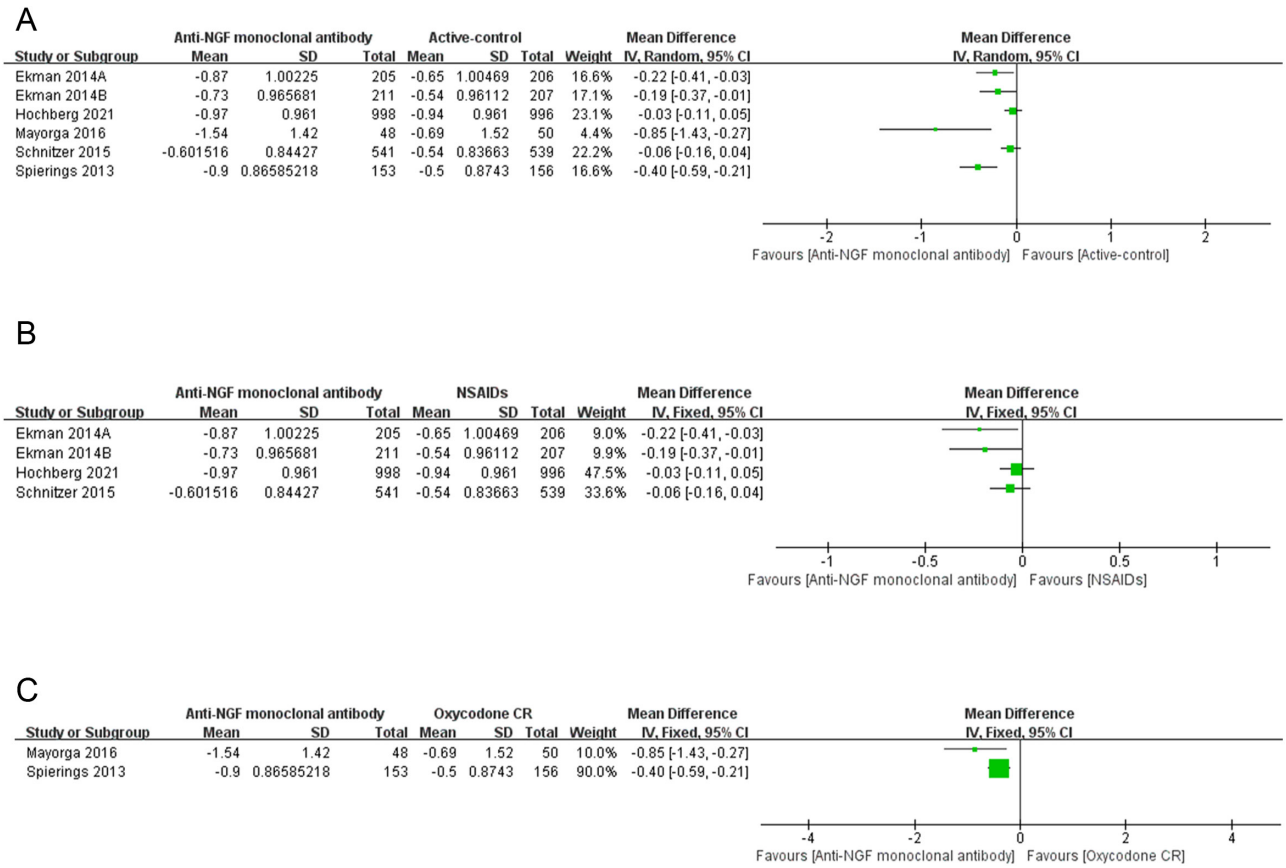

Figure 3

Forest plot of patient's global assessment detailing mean differences and 95% CIs comparing anti-NGF monoclonal antibody treatment with active control (A), mean differences and 95% CIs comparing anti-NGF monoclonal antibody treatment with NSAIDs (B), mean differences and 95% CIs comparing anti-NGF monoclonal antibody treatment with oxycodone CR (C). CR, controlled release; IV, inverse variance; NSAIDs, nonsteroidal anti-inflammatory drugs.

had a lower incidence of cardiovascular and gastrointestinal SAEs than NSAIDs (0.4% vs 1.1%). Although only two RCTs (17, 18) reported results for RPOA and only one RCT (18) was statistically significant, tanezumab was suggested to significantly increase the incidence of RPOA compared with placebo in OA patients (21). Consequently, the higher incidence of RPOA with anti-NGF monoclonal antibody treatment is still of concern.

The remarkable efficacy of anti-NGF monoclonal antibodies in the treatment of hip or knee OA is very promising. However, because of safety risks and an inadequate plan to manage them, the FDA and the European Medicines Agency adopted a negative opinion for the anti-NGF monoclonal antibody (tanezumab) marketing authorization application. As a result, it is undeniable that its safety remains the current focus of attention. Notably, one RCT (18) reported the incidence of RPOA and excluded predetermined imaging evidence of specific bone or joint safety (such as RPOA, atrophic OA, subchondral insufficiency fracture, primary osteonecrosis, or pathologic fracture). However, the final result of this study showed that there was still an increased risk of RPOA. At present, the pathological mechanism of RPOA caused by NGF inhibitors is still unclear. It has been reported that NGF promotes tissue repair and may play an important role in preventing deleterious changes by regulating chondrocyte proliferation and differentiation through increased NGF expression. However, inhibition of NGF can adversely affect bone remodeling (22, 23). Another explanation of the pathological mechanism of NGF inhibitors is analgesic neuropathy, in which the analgesic effect of anti-NGF drugs is obvious, which may increase the load of the degenerative part of the involved joint (7). Some scholars also believe that it may be neuropathic neuropathy in which loss of pain ability leads to abnormal joint load, as NGF may play a role in the regulation of nerve sensory neurons (24). However, there is a lack of sufficient evidence for these mechanisms.

NGF can promote the expression of ion channels and neuropeptides in neurons through TrkA and P75 receptor

Table 2 The safety outcomes (anti-NGF monoclonal antibody treatment vs active comparator).

Outcome measures	Hochberg *et al.* (18)[a]			Schnitzer *et al.* (19)[a]			Ekman *et al.* (16)[a]			Ekman *et al.* (16)[a]			Spierings *et al.* (20)[b]			Mayorga *et al.* (17)[b]		
	Outcome	RR (95% CI)	*P* value	Outcome	RR (95% CI)	*P* value	Outcome	RR (95% CI)	*P* value	Outcome	RR (95% CI)	*P* value	Outcome	RR (95% CI)	*P* value	Outcome	RR (95% CI)	*P* value
Withdrawal due to adverse events	8.8% vs 5.2%	1.69 (1.21, 2.35)	0.002	12.0% vs 9.1%	1.32 (0.93, 1.88)	0.12	6.3% vs 6.3%	1.00 (0.48, 2.10)	1.00	1.9% vs 7.6%	0.25 (0.08, 0.74)	0.01	1.2% vs 10.1%	0.12 (0.03, 0.52)	0.005	14.6% vs 16.0%	0.91 (0.36, 2.32)	0.85
Severe adverse events	11.0% vs 6.6%	1.66 (1.24, 2.23)	0.0006	8.1% vs 8.0%	1.02 (0.68, 1.53)	0.93	3.4% vs 2.4%	1.40 (0.45, 4.34)	0.56	1.4% vs 4.3%	0.33 (0.09, 1.21)	0.1	2.5% vs 2.5%	0.98 (0.25, 3.86)	0.98	0% vs 4.0%	0.21 (0.01, 4.23)	0.31
Rapidly progressive OA	6.3% vs 1.2%	5.24 (2.84, 9.65)	< 0.00001	-	-	-	-	-	-	-	-	-	-	-	-	0.7% vs 0.2%	3.99 (0.45, 35.54)	0.22
Total joint replacement	8.0% vs 2.6%	3.07 (1.99, 4.74)	< 0.00001	4.4% vs 4.6%	0.96 (0.55, 1.65)	0.87	0.5% vs 0%	3.00 (0.12, 73.22)	0.50	0% vs 0.5%	0.33 (0.01, 8.14)	0.50	-	-	-	0% vs 2%	0.35 (0.01, 8.31)	0.51
Abnormal peripheral sensation	3.2% vs 1.4%	2.28 (1.22, 4.25)	0.009	10.7% vs 5.8%	1.86 (1.23, 2.84)	0.004	11.7% vs 8.3%	1.41 (0.78, 2.55)	0.25	10.9% vs 4.3%	2.56 (1.21, 5.39)	0.01	8.1% vs 2.5%	3.19 (1.06, 9.57)	0.04	10.4% vs 16.0%	0.65 (0.23, 1.85)	0.42
CV and GI events	0.4% vs 1.0%	0.40 (0.13, 1.27)	0.12	5.0% vs 6.5%	0.77 (0.47, 1.25)	0.29	1.5% vs 5.3%	0.27 (0.08, 0.96)	0.04	2.4% vs 7.6%	0.31 (0.12, 0.84)	0.02	6.8% vs 43.7%	0.16 (0.09, 0.28)	< 0.00001	22.9% vs 62.0%	0.37 (0.21, 0.65)	0.0005

[a]anti-NGF monoclonal antibody treatment vs NSAIDs; [b]anti-NGF monoclonal antibody treatment vs oxycodone CR.
CR, controlled-release; CV, cardiovascular; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; RR, relative risk.

signaling to pain receptors, which contributes to the innervation of the joint microenvironment. Moreover, given that the growth of nerves and the growth of blood vessels are consistent with each other, pain receptors can regulate blood flow. Inhibition of NGF signaling and subsequent neuronal signaling, as well as the relatively rapid reversal from enhanced NGF signaling to almost complete loss of NGF signaling in OA, may lead to dramatic changes in blood flow and innervation, resulting in changes in the microenvironment of the joint, thus damaging the joint (25). However, more research is needed on the interaction between the vascular nervous system and the rest of the joint microenvironment. In addition, phenotypes of patients were studied in a postanalysis of data from a clinical trial of tanezumab for OA. The researchers found that two serum biomarkers, namely, C3M (a marker of synovial-tissue inflammation) and C2M (a marker of cartilage degeneration), predicted type 2 RPOA for those who used NSAIDs for less than 90 days (71% accuracy) and that individuals with this biomarker phenotype had an eightfold higher risk of developing RPOA than OA patients who did not have this phenotype (26). While further clinical validation is needed, studying the phenotype of OA patients who may be at risk for RPOA will help clinicians identify patients with OA who would benefit most and minimize risk from treatment with anti-NGF monoclonal antibodies. In addition, it has been suggested that the incidence of RPOA may be related to the dose of anti-NGF monoclonal antibodies (27). However, due to current data limitations, we included only a moderate dose of anti-NGF monoclonal antibodies compared with active interventions. Further studies are needed to determine whether a lower dose of anti-NGF monoclonal antibodies will reduce the incidence of RPOA in comparison to active interventions while still maintaining a good effect.

One cost-effectiveness analysis of anti-NGF found that because anti-NGF treatment provided sufficiently pronounced pain relief, even if 10% of the patients developed RPOA, it does not offset the overall improvement in quality-adjusted life years achieved and that the cost of anti-NGF therapy may be as low as $400 per dose (28). It is important to note that these analyses are based on the use of an arbitrary-value model of pain-related costs (29). Clinicians need to be comprehensively considered, as individuals may have different perspectives on risks and benefits.

In terms of abnormal peripheral sensation, more than half of the RCTs reported a higher incidence with anti-NGF monoclonal antibody treatment. However, most of these cases are short-term without any permanent sequelae, sensory impairment disappears within 1–2 weeks or a month after the first dose, and the severity of the condition is usually rated as mild or moderate (30, 31, 32, 33). Overall, most patients with new or worsening

peripheral neuropathy are diagnosed with some form of mononeuropathy (mainly carpal tunnel syndrome) or radiculopathy based on diagnostic tests or significant clinical signs, and few patients are diagnosed with polyneuropathy (20, 34, 35, 36). Neurosensory symptoms induced by anti-NGF therapy may be caused by reversible functional changes or homeostasis of peripheral nerve activity. In addition, anti-NGF monoclonal antibody did not show obvious abnormal findings of cardiovascular, liver, kidney or gastrointestinal function or other laboratory tests (16, 19). Therefore, anti-NGF monoclonal antibody treatment is generally safe in terms of neurological effects.

The pharmacological mechanism of NSAIDs mainly involves inhibition of the activity of cyclooxygenase (COX), which is necessary for the synthesis of prostaglandin (PG), preventing the synthesis of PG and thus leading to analgesic and anti-inflammatory effects. COX includes COX-1 and COX-2, which have opposite effects. With greater inhibition of COX-1, a drug will have fewer cardiovascular and cerebrovascular AEs but more adverse reactions related to the digestive tract and kidneys. In contrast, with greater inhibition of COX-2, a drug will have fewer adverse reactions related to the digestive tract, but the cardiovascular and cerebrovascular AEs caused by the lack of inhibition of COX-1 and thromboxane A2 (TXA2) on platelets are particularly prominent (37). Thus, among NSAIDs, nonselective COX inhibitors and specific COX-2 inhibitors can produce significant adverse effects. Most elderly patients are at high risk of gastrointestinal and cardiovascular diseases, and hip or knee OA predominantly affects the elderly population, thus limiting the use of NSAIDs. Our study also found that NSAIDs had significantly higher rates of gastrointestinal and cardiovascular AEs than anti-NGF monoclonal antibody treatment. The incidence of cardiovascular and gastrointestinal SAEs with NSAIDs was also higher than that with anti-NGF monoclonal antibody treatment (1.1% vs 0.4%). In addition, the many AEs and global abuse of opioids have become urgent issues to be addressed (38, 39). Therefore, to further ameliorate the problems associated with opioids and among patients with more severe gastrointestinal and cardiovascular disease, anti-NGF monoclonal antibodies might be an alternative treatment option for hip or knee OA.

Some limitations of this review are worth noting. First, although the overall sample size was large and the overall quality of the included studies was relatively high, this study design resulted in a systematic review of relatively few studies (six RCTs). Second, only two RCTs were included for the risk assessment of RPOA, and more studies still need to be conducted in the future. Third, at present, there is inconsistency among the outcomes of several safety assessments of anti-NGF monoclonal antibody treatment and active comparator therapy. Most of the included RCTs had a short follow-up period, with only two studies having a follow-up period of more than 48 weeks. Finally, the lack of sufficient data prevented detailed stratification of different doses. Therefore, more long-term studies are needed to evaluate the efficacy and safety of different doses of anti-NGF monoclonal antibody treatment compared to those of analgesic drugs.

Conclusion

Based on recent research evidence, anti-NGF monoclonal antibodies are not yet a replacement for analgesic drugs such as NSAIDs but might be a new treatment option for hip or knee OA patients who are intolerant or unresponsive to nonopioid or opioid treatment. Notably, however, considering the inconsistency and inconclusive evidence on the safety outcomes of recent studies, more research with long-term follow-up is required.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EOR-21-0103.

ICMJE Conflict of Interest Statement

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this manuscript.

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