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Relative Efficacy and Safety of Tanezumab for Osteoarthritis

A Systematic Review and Meta-analysis of Randomized-Controlled Trials

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Objectives: The aim of this meta-analysis was to evaluate the efficacy and safety of tanezumab for the treatment of patients with knee or hip osteoarthritis (OA).

Methods: PubMed, Embase, Cochrane Central Register of Controlled Trials, and Web of Science were searched from inception to July 2020. Randomized-controlled trials comparing tanezumab with placebo or nonsteroidal anti-inflammatory drugs in patients with OA. Two investigators identified studies and independently extracted data, and conventional meta-analyses were conducted with Review Manager 5.3. The outcomes were pain relief, functional improvement, and risk of adverse events (AEs).

Results: A total of 8 articles, comprising 9 randomized-controlled trials, were included. Overall, tanezumab was superior to placebo for relieving pain and improving function, as well as in the patient's global assessment. Tanezumab also had significant advantages over nonsteroidal anti-inflammatory drugs for relieving pain and improving function, as well as in the patient's global assessment. Significantly more patients discontinued treatment because of AEs after treatment with tanezumab. However, the differences in serious AEs and total joint replacement were not significant. Moreover, tanezumab-treated patients experienced significantly more rapid progression of osteoarthritis.

Discussion: Tanezumab can alleviate pain and improve function for patients with OA of the hip or knee. Although tanezumab does not cause serious AEs, rapid progression of OA occurred in a small number of participants, so more clinical trials are needed to explore its safety.

Key Words: osteoarthritis, tanezumab, meta-analysis, randomized-controlled trials

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Osteoarthritis (OA) is the most common form of arthritis, affecting ~302 million people worldwide, and is a cause of disability in the elderly.[1] OA is characterized by pathology involving the whole joint, including cartilage degradation, bone remodeling, osteophyte formation, and synovial inflammation, leading to pain, stiffness, swelling, and loss of normal joint function.[2] Pain is the main symptom of OA, which seriously affects the patient's quality of life. Pain accounts for large societal costs and morbidity across all societies and is clearly inadequately controlled with current biomedical and psychosocial strategies. At present, nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line drugs to treat OA. However, these drugs can cause serious adverse events (SAEs), such as gastrointestinal bleeding, peptic ulcers, and cardiovascular effects, and the pain relief effect of NSAIDs is not obvious in the treatment of severe pain.[3]

In recent years, neurotrophic factors, which are secreted proteins that promote the growth and survival of neurons, have received increasing attention as novel targets for the treatment of chronic pain; examples of neurotrophic factors include nerve growth factor (NGF), brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin-4.[4] By far, the most advanced strategy to target neurotrophic factors for OA pain is the approach that uses neutralizing antibodies against NGF. NGF has become an important target for developing analgesics because of the well-documented role of NGF in pain, as it has been found to be highly overexpressed in human pain states, including OA.[5] Tanezumab, a humanized monoclonal antibody, specifically targets and inhibits NGF from binding with its receptors, neurotrophic tyrosine kinase receptor type 1 and p57. At present, there are some clinical trials using tanezumab to treat OA, and they have achieved good results in analgesia and functional improvement, but rapidly progressive osteoarthritis (RPOA) occurred in a small number of participants.[6]

Previously, there have been 3 meta-analyses on the treatment of OA with tanezumab.[7–9] Their results suggested

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B.Z. and X.T.: carried out the literature search and statistical analysis; collected, analyzed, and interpreted the data; wrote the manuscript. Z.Q.: resolved differences and performed statistical analysis. J.L.: wrote and critically revised the manuscript. L.Y.: led the design and contributed to language correction.

The authors declare no conflict of interest.

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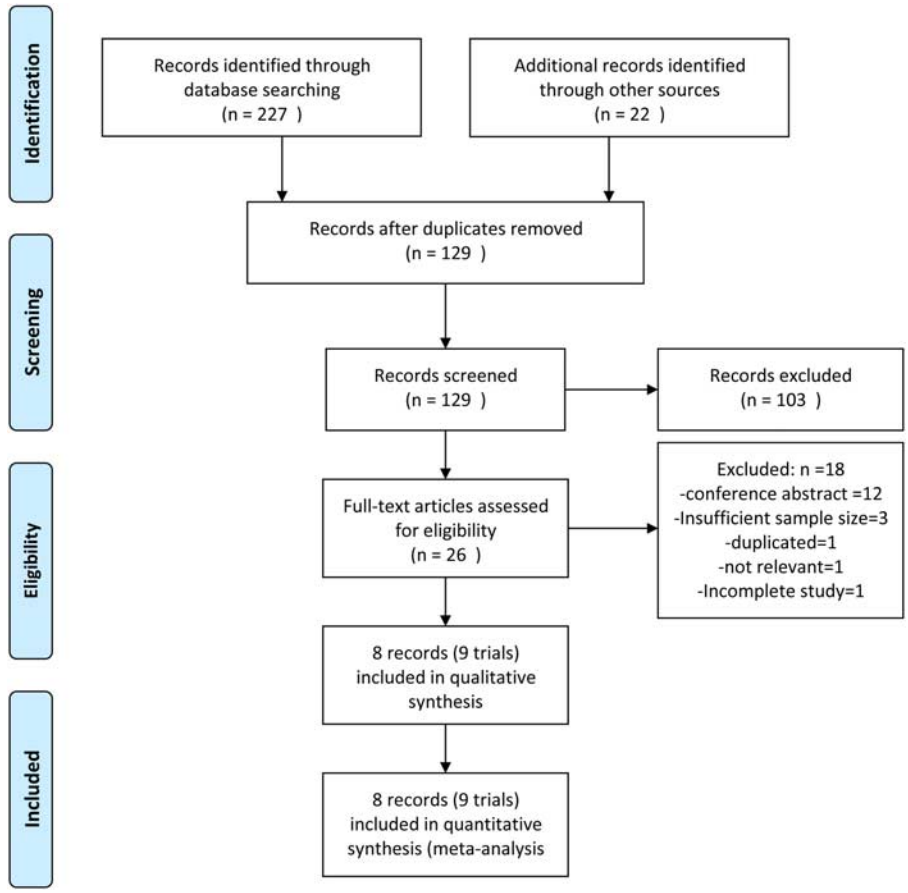

FIGURE 1. Preferred reporting items for systematic reviews and meta-analysis flowchart for the searching for and identifying included studies.

that tanezumab had obvious advantages over placebo or NSAIDs in analgesia and functional improvement, but the relationship between tanezumab and RPOA has not been analyzed. Therefore, the goal of our meta-analysis was to combine the results of previous clinical trials to analyze the effectiveness and safety of tanezumab in the treatment of OA and to further analyze the correlation between tanezumab and RPOA events.

METHODS

Protocol and Registration

This systematic review and meta-analysis study was implemented following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[10] and the protocol was registered with Prospero, an international prospective register of systematic reviews (CRD42020200793).

Search Strategy

We systematically searched the Cochrane Central Register of Controlled Trials, PubMed, Embase and Web of Science (from inception to July 15, 2020) using a combination of relevant terms, including tanezumab, osteoarthrosis, placebo, and randomized-controlled trial (RCT), without restrictions on the language (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/CJP/A826). Ongoing and unpublished studies were searched in the clinical trial registry (ClinicalTrials.gov). In addition, references of the retrieved papers and reviews were manually reviewed.

Inclusion/Exclusion Criteria

The inclusion criteria were as follows: (1) RCTs with an average of at least 100 participants per arm[11]; (2) studies on only participants with OA of the hip or knee according to the American College of Rheumatology criteria and grade 2 or higher based on the Kellgren-Lawrence grading system[12,13]; (3) studies comparing tanezumab at any dose and any route with placebo or NSAIDs; (4) studies reporting pain (Western Ontario and McMaster Universities (WOMAC) pain, function (WOMAC physical functional), patient's global assessment (PGA) or AEs (RPOA events, total joint replacement [TJR]) events, patients who discontinued treatment because of adverse events (AE) and SAE outcomes; and (5) studies published in any language.

The following studies were excluded: (1) secondary analyses, including pooled analyses; (2) studies where the follow-up time was <1 week; (3) studies using tanezumab combined with other drugs; (4) studies for pain in the joints caused by other conditions such as rheumatoid arthritis or other autoimmune disorders and postoperative pain; and (5) abstracts only (insufficient data).

Study Selection and Data Extraction

The selection of literature and decisions about including studies were carried out independently by 2 review

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TABLE 1. Characteristics of the Included Comparisons in RCTs and the Results of Conventional Meta-analysis

References	Funding Source	Design	Study Duration (wk)	No. Randomized and Treated (N on Tanezumab)	Joint Affected	Primary Outcome Extracted	NCT Number
Berenbaum et al[33]	Commercial	Multicentre, Parallel	48	849 (567)	Hip or knee	WOMAC pain, WOMAC physical function, PGA	NCT02709486
Brown et al[34]	Commercial	Parallel	32	690 (518)	Knee	WOMAC pain, WOMAC physical function, PGA	NCT00733902
Brown et al[35]	Commercial	Parallel	32	621 (466)	Hip	WOMAC pain, WOMAC physical function, PGA	NCT00744471
Ekman et al[36]	Commercial	Parallel	24	828 (414)	Knee	WOMAC pain, WOMAC physical function, PGA	NCT00830063
Ekman et al[36]	Commercial	Parallel	24	840 (420)	Hip or knee	WOMAC pain, WOMAC physical function, PGA	NCT00863304
Schnitzer et al[38]	Commercial	Multicentre, Parallel	16	2700 (1083)	Hip or knee	WOMAC pain, WOMAC physical function, PGA	NCT00809354
Schnitzer et al[39]	Commercial	Multicentre, Parallel	16	696 (464)	Hip or knee	WOMAC pain, WOMAC physical function, PGA	NCT02697773
Spierings et al[40]	Commercial	Multicentre, Parallel	18	610 (311)	Hip or knee	WOMAC pain	NCT00985621
NCT02528188	Commercial	Multicentre, Parallel	80	2996 (2000)	Hip or knee	WOMAC pain, WOMAC physical function, PGA	NCT02528188

NCT indicates national clinical trial; PGA, patient's global assessment; RCT, randomized-controlled trial; WOMAC, The Western Ontario and McMaster Universities.

authors (B.Z. and X.T.). We obtained the full text for the studies to determine inclusion in our review. If there were multiple reports that described the same trial, only the most recent or complete study was included.

Relevant data from selected studies were independently extracted according to inclusion criteria by 2 review authors (B.Z. and X.T.). The following data were extracted: author, published year, type of funding support, duration of study, study design, sample size, types of joints affected, and types of measures used for the outcomes. We also extracted data from participants at baseline, including sex, mean age, dose of tanezumab, route of administration, and type of control used. A third review author (Z.Q.) resolved any disagreements about study selection and data extraction.

The primary outcome measures of interest were mean change in the WOMAC pain, the WOMAC physical function, and the PGA at the baseline and endpoint. The secondary outcome measures comprised patients who discontinued treatment because of AEs, number of SAEs, RPOA events, and TJR events. If the mean, SD or standard error of the mean were not attainable in the text of the articles, we extracted values from the diagrams and tables as needed.[14]

Quality Assessment

Two review authors (B.Z. and X.T.) independently assessed the risk of bias for each study using the Cochrane risk of the bias assessment tool.[14] The tool includes seven specific domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and "other sources of bias." Each domain was assigned a score of low risk of bias, high risk of bias or unclear risk of bias. We resolved disagreements by consensus.

Statistical Analysis

A conventional meta-analysis was conducted to compare tanezumab with placebo or NSAIDs using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). We used risk ratios (RRs) and 95% confidence intervals (CIs) for dichotomous data based on the number of events in the control and intervention groups of each study. For continuous data, we calculated the mean differences (MDs) and 95% CIs between the tanezumab and control groups. WOMAC pain and WOMAC physical function scores were converted to a common scale from 0 (no pain or disability) to 10 (worst possible pain or disability) before meta-analysis. The heterogeneity of the effect size across the studies was tested using the χ^2 test ($P<0.1$ was considered heterogeneous) and I^2 statistic ($I^2>50\%$ was considered heterogeneous). If there was significant heterogeneity between studies, a random-effects model was used; otherwise, a fixed-effects model was used. Subgroup analysis was based on the dose of tanezumab and the type of control group. The overall effect was tested using a Z score with the significance set at $P<0.05$. We used funnel plots to assess publication bias if more than 10 trials were included in any particular pooled analysis.

RESULTS

Study Selection

The PRISMA flowchart of study selection is shown in Figure 1. We identified 227 studies from database searches and 22 additional records from other sources. After

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TABLE 2. Baseline Patient Characteristics

References	Intervention	N	Age (y)	Female (%)	Duration Since Diagnosis (y)	Kellgren-Lawrence Grade (%)		
						2	3	4
Berenbaum et al[33]	Tan (2.5 mg, SC)	283	65.2	198 (70.0)	6.0	49 (17.3)	131 (46.3)	101 (35.7)
	Tan (5 mg, SC)	284	65.2	193 (68.0)	6.7	58 (20.4)	121 (42.6)	105 (37.0)
	Placebo	282	64.2	196 (69.5)	7.4	59 (20.9)	123 (43.6)	100 (35.5)
Brown et al[34]	Tan (2.5 mg, IV)	172	60.8	94 (54.7)	7.3	64 (37.2)	74 (43.0)	31 (18.0)
	Tan (5 mg, IV)	172	62.1	101 (58.7)	7.5	64 (37.2)	89 (51.7)	18 (10.5)
	Tan (10 mg, IV)	174	61.4	106 (60.9)	9.5	71 (40.8)	77 (44.3)	26 (14.9)
	Placebo	172	62.2	119 (69.2)	8.2	68 (39.5)	82 (47.7)	22 (12.8)
Brown et al[35]	Tan (2.5 mg, IV)	155	62.4	101 (65.2)	6.0	71 (45.8)	53 (34.2)	31 (20.0)
	Tan (5 mg, IV)	154	61.8	92 (59.7)	6.3	72 (46.8)	54 (35.1)	27 (17.5)
	Tan (10 mg, IV)	157	63.3	88 (56.1)	5.6	67 (42.7)	58 (36.9)	32 (20.4)
	Placebo	155	61.9	103 (66.5)	5.6	73 (47.1)	56 (36.1)	26 (16.8)
Ekman et al[36]	Tan (5 mg, IV)	206	61.1	122 (59.2)	7.9	76 (36.9)	108 (52.4)	22 (10.7)
	Tan (10 mg, IV)	208	61.1	128 (61.5)	8.5	98 (47.1)	90 (43.3)	20 (9.6)
	Naproxen	206	61.4	129 (62.6)	7.2	99 (48.1)	89 (43.2)	18 (8.7)
	Placebo	208	60.9	120 (57.7)	9.0	89 (42.8)	91 (43.8)	28 (13.5)
Ekman B et al[36]	Tan (5 mg, IV)	211	59.8	134 (63.5)	6.4	104 (49.3)	77 (36.5)	30 (14.2)
	Tan (10 mg, IV)	209	59.2	128 (61.2)	6.8	101 (48.3)	72 (34.4)	36 (17.2)
	Naproxen	211	60.3	136 (64.5)	7.7	110 (52.1)	84 (39.8)	17 (8.1)
	Placebo	209	60.1	136 (65.1)	6.3	107 (51.2)	79 (37.8)	22 (10.5)
Schnitzer et al[38]	Tan (5 mg, IV)	541	61.9	392 (72.5)	7.3	181 (33.5)	191 (35.3)	169 (31.2)
	Tan (10 mg, IV)	542	62.0	392 (72.3)	7.1	187 (34.5)	203 (37.5)	152 (28.0)
	Tan+NSAID*	536	61.7	363 (67.7)	7.0	183 (34.2)	212 (39.6)	139 (26.0)
	Tan+NSAID*	542	61.3	369 (68.1)	7.4	161 (29.7)	218 (40.2)	163 (30.1)
	Placebo+NSAID*	539	61.3	388 (72.0)	7.5	197 (36.5)	217 (40.3)	125 (23.2)
Schnitzer et al[39]	Tan (2.5 mg, SC)	231	60.9	145 (62.8)	6.4	60 (26.0)	101 (43.7)	69 (29.9)
	Tan (2.5/5 mg, SC)	233	61.2	151 (64.8)	7.2	59 (25.4)	105 (45.3)	68 (29.3)
	Placebo	232	60.4	157 (67.7)	6.9	65 (28.0)	98 (42.2)	69 (29.7)
Spierings et al[40]	Tan (5 mg, IV)	161	57.8	96 (59.6)	7.6	78 (48.4)	60 (37.3)	23 (14.3)
	Tan (10 mg, IV)	150	57.0	94 (62.7)	7.5	73 (48.7)	55 (36.7)	22 (14.7)
	Oxycodone	158	57.6	99 (62.7)	6.2	80 (50.6)	55 (34.8)	23 (14.6)
	Placebo	141	57.2	92 (65.2)	7.4	67 (47.5)	56 (39.7)	18 (12.8)
NCT02528188 (unpublished)	Tan (2.5 mg, SC)	1002	60.3	637 (63.6%)	None	None	None	None
	Tan (5 mg, SC)	998	61.2	654 (65.5)	None	None	None	None
	Placebo+NSAID†	996	60.3	662 (66.5)	None	None	None	None

*Naproxen or celecoxib.
†Naproxen, celecoxib or diclofenac.
IV indicates intravenously; NCT, national clinical trial; NSAID, nonsteroidal anti-inflammatory drug; SC, subcutaneously; Tan, tanezumab.

removing duplicates, we assessed 129 studies and excluded 106 studies based on the titles and abstracts. We assessed the full text of 26 possibly eligible papers, and excluded studies included 12 conference abstracts,[15–26] 3 papers with an insufficient sample size,[27–29] 1 duplicate study,[30] 1 not relevant study,[31] and 1 incomplete study.[32] Finally, we included 8 eligible papers (9 studies) in the quantitative analysis and meta-analysis.[33–40]

Study Characteristics

The characteristics of the included studies are shown in Table 1, and the details of the baseline patient characteristics are shown in Table 2. This review includes 8 papers reporting 9 RCTs and has a sample size of 10830 participants. A total of 6243 patients were included in the intervention group. One record reported on the results of 2 separate RCTs.[36] One record provided results posted online but not published in a peer-reviewed journal.[37] All studies were phase III clinical trials, and patients in the intervention group received 2.5/5/10 mg tanezumab every 8 weeks, administered intravenously or subcutaneously. The control groups were placebo, NSAIDs (naproxen or celecoxib) and oxycodone, but oxycodone did not meet the inclusion criteria, so we excluded the oxycodone group in this review. The duration of the studies was 16 to 80 weeks. Only knee, hip or both knee and hip OA were evaluated in the included studies. In 2 studies, only the knee joint was evaluated.[34,36] The hip joint was evaluated in 1 study.[36] The remaining studies included both the hip and knee joints simultaneously. All studies reported receiving funding from pharmaceutical companies that produced study drugs. All studies were registered on the ClinicalTrials.gov website.

Risk of Bias Among the Included Studies

The risk of bias assessment for all of the studies is shown in Figure 2. All studies had 2 or more domains that were judged as having an unclear risk of bias. Randomized sequence generation was implemented adequately in 3 studies,[33,38,39]

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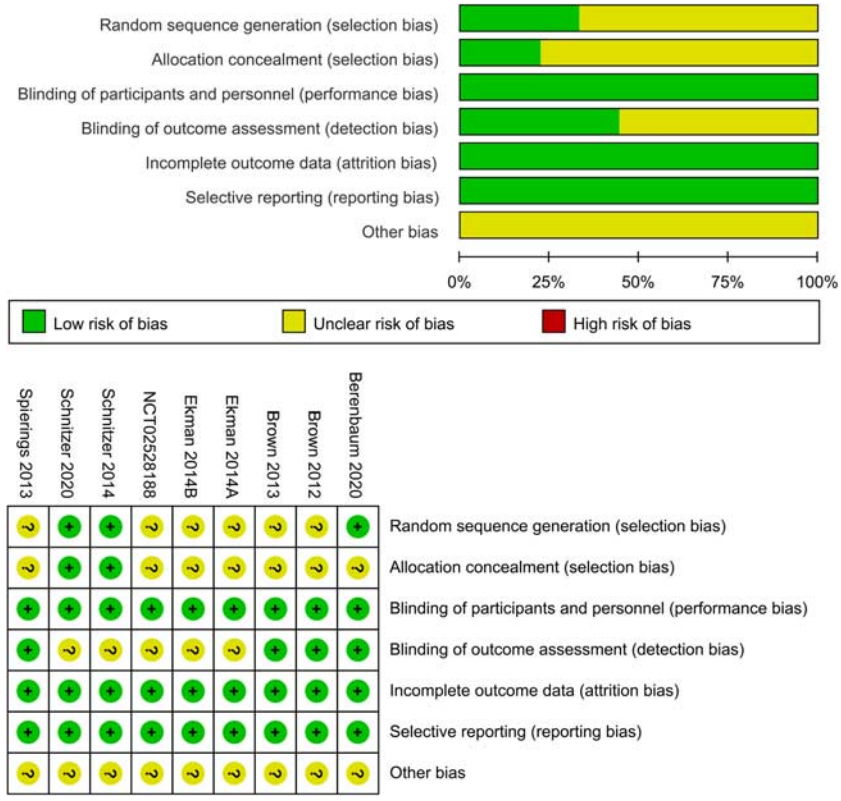

FIGURE 2. Risk of bias in the selected studies.

although all of them reported being RCTs. Allocation concealment was implemented adequately in 2 studies.[38,39] All included studies successfully reported blinding of participants, and personnel were at low risk of performance bias. Four studies reported blinding of outcome assessors at unclear risk of bias of detection bias.[33–35,40] All studies were funded by companies that produced tanezumab and were at unclear risk of bias for the other sources of domain bias. Visual cues in funnel plots indicated that there was no conclusive evidence of publication bias (Supplementary Fig. 1, Supplemental Digital Content 2, http://links.lww.com/CJP/A827).

Effects on Joint Pain

All included studies evaluating analgesic efficacy utilized WOMAC pain reduction as the primary or secondary outcome. First, we compared the mean change between the tanezumab group and placebo group. Tanezumab was significantly superior to placebo (MD = −0.91, 95% CI = −1.10 to –0.72, $P < 0.00001$; $I^2 = 0\%$) (Fig. 3). In the subgroup analysis, the effect tended to rise with the increase in the dose of the drug (MDs of −0.66/−0.96/−1.05 at 2.5 mg/5 mg/10 mg, respectively). Similar results were obtained in the tanezumab group and NSAID group (MD = −0.49, 95% CI = −0.66 to –0.31, $P < 0.00001$; $I^2 = 0\%$) (Supplementary Fig. 2, Supplemental Digital Content 3, http://links.lww.com/CJP/A828). The above results showed that tanezumab had superior analgesic effects compared with placebo and NSAIDs.

Effects on Physical Function

All studies reported comprehensive WOMAC physical function outcome data. The WOMAC physical function scores were significantly different between the tanezumab group and placebo group (MD = −0.93, 95% CI = −1.10 to –0.75, $P < 0.00001$; $I^2 = 0\%$) (Fig. 4). In the dose-response subgroup analysis, the 10 mg group had a superior physical function score (MDs of −0.76/−0.94/−1.02 at 2.5 mg/5 mg/10 mg, respectively). Compared with NSAIDs, tanezumab also showed good results in functional improvements (MD = −0.53, 95% CI = −0.71 to –0.35, $P < 0.00001$; $I^2 = 0\%$) (Supplementary Fig. 3, Supplemental Digital Content 4, http://links.lww.com/CJP/A829).

PGA

All studies report data on PGA. PGA of OA was assessed using a 5-point Likert scale (1 = very good and 5 = very poor). The reduction in PGA scores was significantly larger between the tanezumab group and placebo group (MD = −0.31, 95% CI = −0.37 to –0.25, $P < 0.00001$; $I^2 = 0\%$) (Fig. 5). In the dose-response subgroup analysis, as the dose increased, the improvement effect over placebo was more obvious (MDs of −0.21/−0.31/−0.38 at 2.5 mg/5 mg/10 mg, respectively). PGA also showed some improvement in the overall comparison between the tanezumab and NSAID groups (MD = −0.08, 95% CI = −0.14 to –0.02, $P = 0.008$; $I^2 = 0\%$) (Supplementary Fig. 4, Supplemental Digital Content 5, http://links.lww.com/CJP/A830). However, in the subgroup analysis, the PGA improvement was not statistically significant when comparing the 10 mg tanezumab versus NSAIDs (MD = −0.08, 95% CI = −0.18 to –0.01, $P = 0.09$; $I^2 = 0\%$) (Supplementary Fig. 4, Supplemental Digital Content 5, http://links.lww.com/CJP/A830).

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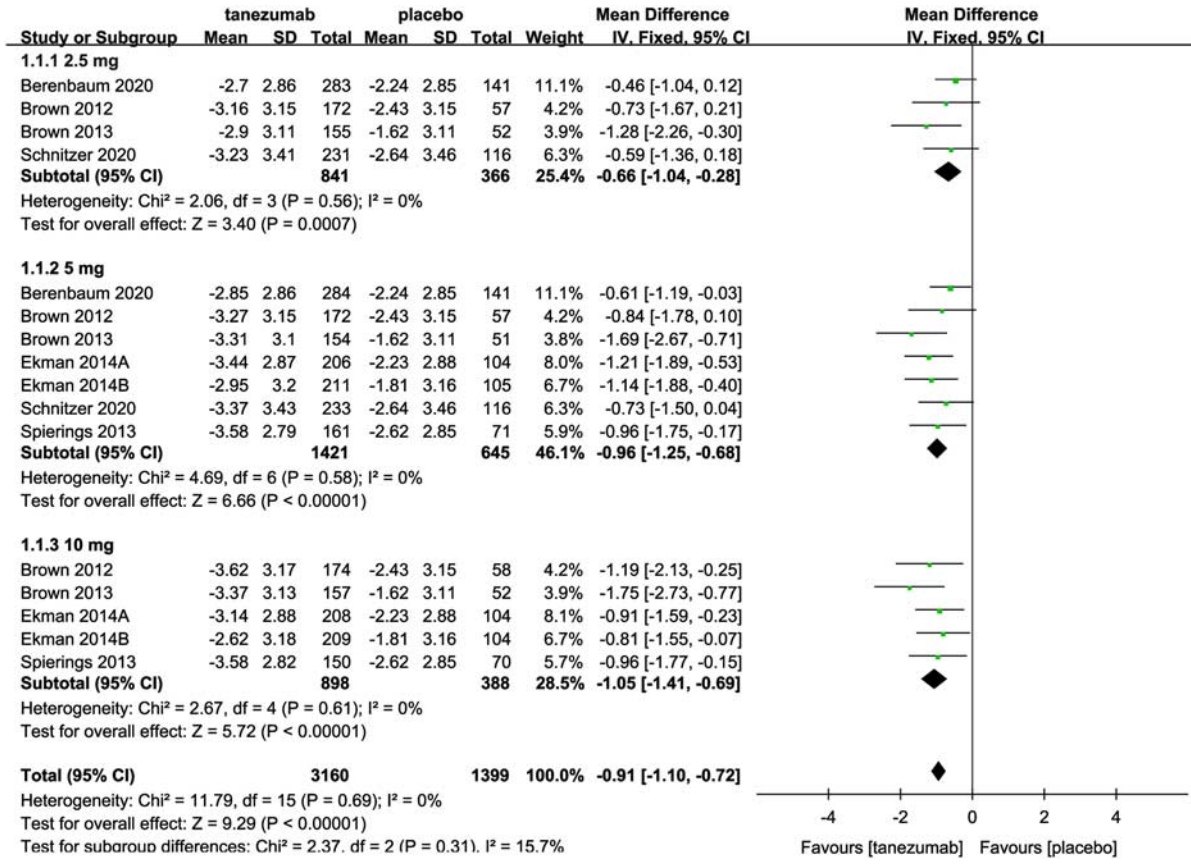

FIGURE 3. Forest plots of the mean change in Western Ontario and McMaster Universities Osteoarthritis Index pain after treatment with tanezumab versus placebo (mean ± SD). CI indicates confidence interval.

Safety

The safety of tanezumab was investigated in 4 aspects: the number of patients who discontinued treatment because of AEs, SAEs, and the number of RPOA events and TJR events. All 9 studies reported patients who discontinued treatment because of AEs and SAEs. Five studies[33,37–40] reported patients who experienced RPOA events, and 8 studies[33–36,38–40] reported patients who experienced TJR events.

Patients Who Discontinued Treatment Because of AEs

The tanezumab group had a significantly increased number of patients who discontinued treatment because of AEs compared with those in the placebo and NSAIDs groups (RR = 1.36, 95% CI = 1.09 to 1.70, $P = 0.006$; $I^2 = 16\%$) (Fig. 6A).

SAEs

SAEs were defined as events resulting in hospitalization (initial or prolonged), disability or permanent damage, congenital abnormality or birth defect of offspring, life-threatening events or death. There were no significant differences in the number of participants reporting SAEs between the tanezumab group and the placebo or NSAIDs group (RR = 1.18, 95% CI = 0.97 to 1.45, $P = 0.53$; $I^2 = 0\%$) (Fig. 6B).

RPOA Events

There were significantly increased RPOA events in the tanezumab group compared with those in the placebo and NSAIDs groups (RR = 9.2, 95% CI = 2.59 to 32.71, $P = 0.0006$; $I^2 = 0\%$) (Fig. 6C). In the subgroup analysis, we found that the incidence of RPOA was the highest in the 5 mg tanezumab group (RR = 6.49, $P = 0.001$; $I^2 = 0\%$) but was not statistically significant in the 2.5 and 10 mg tanezumab groups compared with that in the control group (Supplementary Fig. 5, Supplemental Digital Content 6, http://links.lww.com/CJP/A831).

TJR

There were no significant differences in the TJR events between the tanezumab group and the placebo or NSAIDs group (RR = 1.04, 95% CI = 0.77 to 1.42, $P = 0.78$; $I^2 = 14\%$) (Fig. 6D).

DISCUSSION

This systematic review and meta-analysis evaluated the safety and effectiveness of tanezumab in the analgesic effect of OA patients, and 9 RCTs with a total of 10,830 participants were included. The 3 different doses of tanezumab, compared with placebo, significantly improved the WOMAC pain, WOMAC physical function, and PGA, and similar results were also obtained for the comparison

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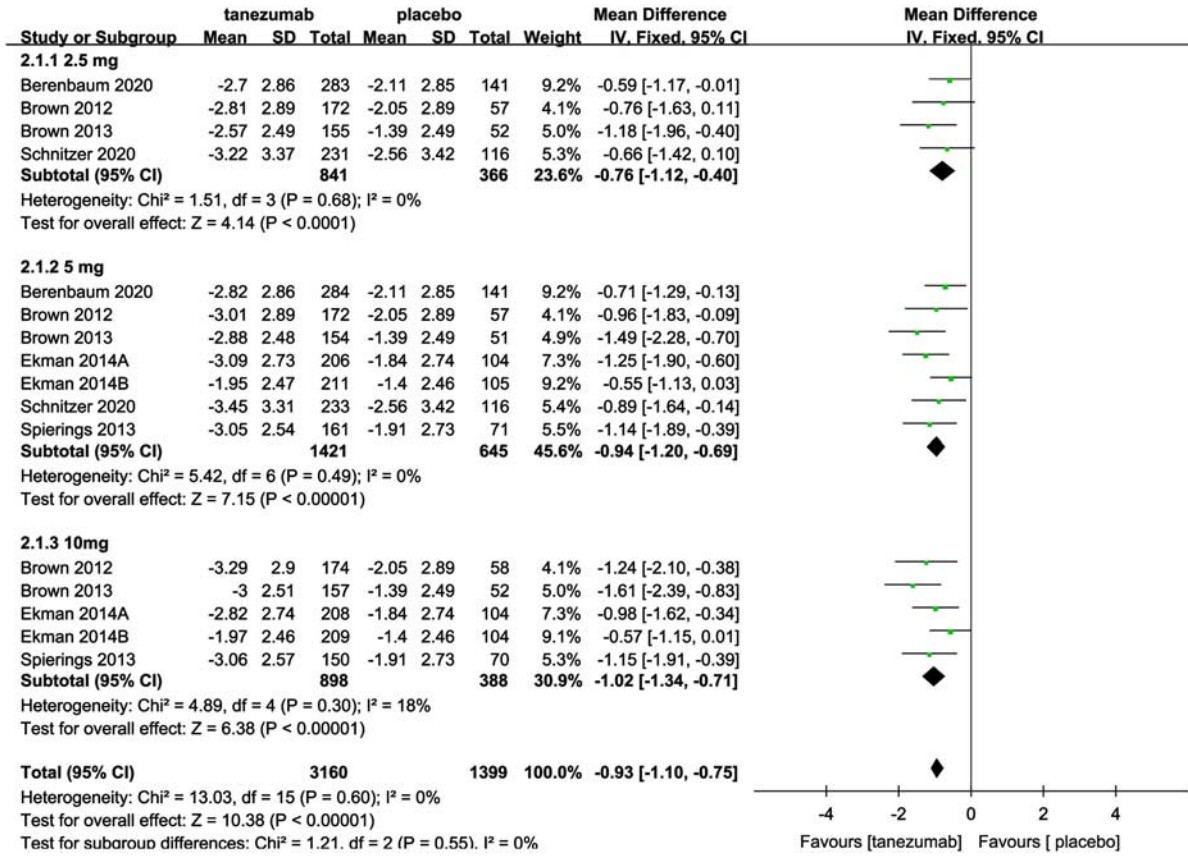

FIGURE 4. Forest plots of mean change in Western Ontario and McMaster Universities Osteoarthritis Index physical function after treatment with tanezumab versus placebo (mean ± SD). CI indicates confidence interval.

of tanezumab with NSAIDs. In the subgroup analysis, we found that compared with placebo or NSAIDs, tanezumab at 10 mg had the best therapeutic effect, but 10 mg of tanezumab, compared with NSAIDs, did not significantly improve the PGA. In the safety evaluation, we found that the occurrence of patients who discontinued treatment because of AEs and experienced RPOA events was significantly higher in the tanezumab group than in the placebo and NSAID groups, and with the increase in the dose of tanezumab, the occurrence of RPOA events also increased. In SAEs and TJR events, there were no significant differences between the intervention group and the control group.

In 2015, a systematic review evaluating the safety of 3 antibodies, namely, tanezumab, fulranumab, and fasinumab, to NGF in the treatment of OA was published.[7] The review included published and unpublished studies of 10 placebo-controlled trials, and 7 involved tanezumab. Efficacy outcomes showed that tanezumab, compared with placebo, resulted in statistically significant improvements in all components of the PGA and the WOMAC scale, including pain and physical function subscales. To obtain an overall view of safety, studies with tanezumab reported a higher rate of patients who discontinued treatment because of AEs in the higher dose groups than in the placebo groups, and the lower dose ranges were similar to those reported with placebo. No significant differences were reported for SAEs between the tanezumab and placebo groups.[7] In 2016 and 2017, 2 meta-analyses obtained similar results on the effectiveness and safety of tanezumab in the treatment of OA.[8,9] On this basis, their results showed that there was a higher incidence of abnormal peripheral sensations and peripheral neuropathy in the tanezumab group than in the placebo group. Compared with results from previous meta-analyses, our results are similar in effectiveness and safety. At the same time, we analyzed the relationship between the use of tanezumab and the occurrence of joint safety incidents, including RPOA and TJR events.

Tanezumab, also known as RN624, in animal models of pain was highly effective at relatively low doses, and controlled animal tolerability and safety studies did not reveal any AEs. On this basis, 2 clinical trials were quickly carried out to test the efficacy of tanezumab in acute or chronic pain. The results of these phase I clinical trials showed that tanezumab has a good analgesic effect on chronic pain and has good safety and tolerability, but the analgesic effect in acute pain is not obvious.[29,41] In 2006, RPOA events occurred in a small percentage of patients, particularly in patients who received concomitant treatment with NSAIDs. The Food and Drug Administration (FDA) imposed a partial clinical hold on noncancer pain-related tanezumab studies because of unexpected AEs.[42] However, there are few studies on the mechanism of RPOA, and there is no effective method to prevent or reduce the occurrence of such AEs. Our analysis results showed that tanezumab has a certain correlation with the occurrence of RPOA in the treatment of OA.

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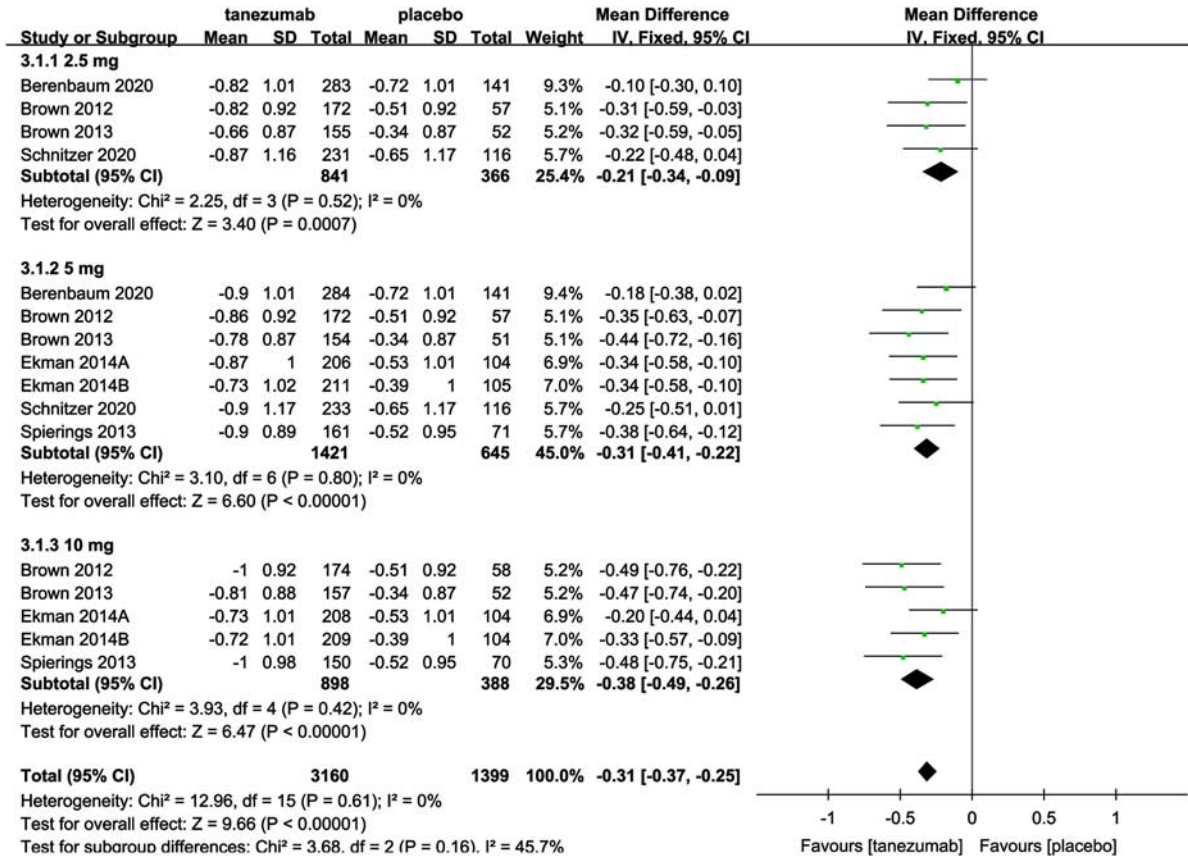

FIGURE 5. Forest plots of the mean change in the patient's global assessment after treatment with tanezumab versus placebo (mean ± SD). CI indicates confidence interval.

RPOA is characterized by pain, with radiographs showing rapid joint space narrowing as a result of chondrolysis and, subsequently, an osteolytic phase with severe progressive atrophic bone that patients with joint space narrowing of ≥ 2 mm per year or loss of > 50% of the joint space within 1 year. RPOA is common in the hip and shoulder joints, and the pathogenesis of RPOA is still unclear. In the included studies, RPOA mainly occurred in weight bearing joints, mainly in the hip and knee. It was previously believed that subchondral fractures and crystal-induced arthritis could lead to the occurrence of RPOA, but these associations have not been experimentally confirmed. In a rat medial meniscal tear model, application of tanezumab could significantly improve the gait but could cause damage to the articular cartilage. In subsequent studies, tibial amputation could significantly improve the cartilage destruction caused by tanezumab. These data suggest that the application of tanezumab for analgesia and a secondary increase in weight bearing cause damage to the articular cartilage.[43] In addition to tanezumab, another anti-NGF called fulranumab also causes RPOA in patients with OA.[44]

In general, tanezumab, compared with placebo or NSAIDs, has obvious advantages in the analgesia and functional improvement of OA. Our analysis also shows that 10 mg of tanezumab has a better therapeutic effect than 5 or 2.5 mg. The risk of RPOA events is the highest in the 5 mg group. A small number of patients on 2.5 mg experienced RPOA events, but this result was not statistically significant compared with placebo. Although the incidence of RPOA in the 10 mg group was not statistically significant compared with that in the control group, this may have been because of the small sample size. In the 10 mg group, there are fewer data on RPOA, and more clinical studies are needed to further verify the experimental results. Therefore, low-dose tanezumab, such as 2.5 mg instead of 5 or 10 mg, should be prioritized in subsequent clinical trials. However, to better use tanezumab to treat OA pain, some experiments are needed to study the mechanism of RPOA. However, this meta-analysis has several limitations. First, most of the follow-up periods of the included studies were relatively short, which created some difficulties in assessing the long-term safety of tanezumab. Second, all included studies received funding from the drug manufacturer, which may have had a certain impact on the results.

CONCLUSIONS

This systematic review identified 8 articles to compare 9 RCTs (10830 patients with OA at the hip or knee joint). Tanezumab reduced pain and improved function in patients with OA. Although tanezumab does not cause SAEs, RPOA occurred in a small number of participants, so more clinical trials are needed to explore its safety. Perhaps in the near future, tanezumab can replace NSAIDs as a new generation of painkillers for the treatment of OA.

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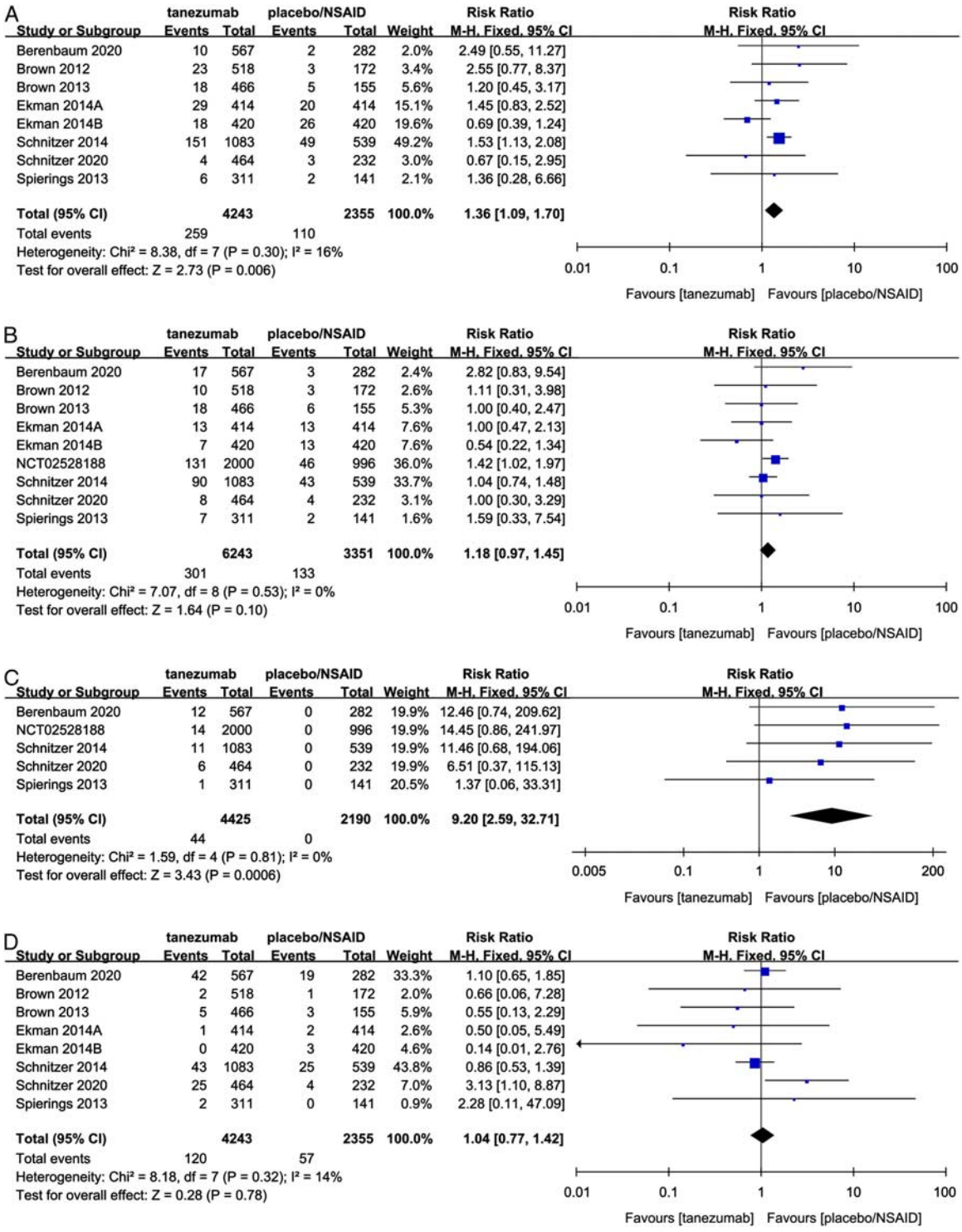

FIGURE 6. Forest plots of the included studies comparing patients who discontinued treatment because of adverse events (A), serious adverse events (B), rapid progression of osteoarthritis (C), and total joint replacement (D) in patients who received tanezumab versus placebo/nonsteroidal anti-inflammatory drugs. CI indicates confidence interval.

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