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Original Research Article

Efficacy and Safety of Tanezumab on Osteoarthritis Knee and Hip Pains: A Meta-Analysis of Randomized Controlled Trials

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Authors J.Y. Chen and J.R. Li contributed equally to this work.

Abstract

Objectives. To evaluate the efficacy and safety of tanezumab for management of osteoarthritis (OA) knee and hip pain.

Methods. Articles about management of OA knee and hip pains by tanezumab were systematically searched in PubMed, EBSCO, EMBASE, ScienceDirect, Web of Science, OVID, and Cochrane Library from the available date of inception until January 2016. Randomized controlled trials (RCTs) comparing the efficacy and safety of tanezumab with placebo/active comparator for management of OA knee and hip pains were included, and those with confounding conditions were excluded. Study quality was assessed using the Jadad five-point score. Finally, a meta-analysis of all eligible RCTs was performed on Review Manager 5.3 and STATA 12.0.

Results. Nine studies with 10 RCTs that enrolled 7,665 patients were included. The reductions in pain intensity are significantly different between tanezumab-treated patients and placebo-treated patients (5,879 patients, mean difference [MD] = -0.98, 95% confidence interval [CI] = -1.18– -0.79). Both functional improvement (6,078 patients, MD = −1.10, 95% CI = −1.28– -0.92) and Patient's Global Assessment (PGA; 5,366 patients, MD = -0.27, 95% CI = -0.34– -0.20) are significantly different. There are significantly more discontinued patients due to adverse events (AEs) after treatment with tanezumab (6,537 patients, risk ratio = 1.62, 95% CI = 1.29–2.03). However, differences in serious AEs are not significant. Moreover, tanezumab-treated patients suffer from significantly more paraesthesia, arthralgia, hypoaesthesia, and peripheral edema.

Conclusions. Tanezumab vs placebo provides superior pain relief and improvement in physical function and PGA in knee and hip osteoarthritis patients and is generally well tolerated with acceptable AEs. Low-dose tanezumab (10 or 25 μg/kg and 2.5 mg) provides similar effectiveness in reducing pain and improving function and is associated with fewer AEs. The long-term safety of tanezumab on osteoarthritis knee and hip pain needs further investigation.

Key Words. Tanezumab; Nerve Growth Factor; Osteoarthritis; Meta-Analysis; Randomized Controlled Trials

Introduction

Osteoarthritis (OA) is the most common form of arthritis in older individuals and the leading cause of disability worldwide [1]. The incidence rate of OA among adults in the United States is about 12%, which is expected to increase over the coming years as the elderly population

booms [2]. Pain intensity is a better predictor of the OA-associated disability degree compared with radiographic severity of disease. As the leading symptom of OA, pain is often chronic, leading to significant morbidity and decreased quality of life. Thus, pain reduction and functional improvement are most important in the treatment of OA. Some guidelines recommend both nonpharmacological and pharmacological therapies for treatment of OA-related pain [3]. Pharmacological management, such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids, is commonly used for painful OA. However, reservations have been expressed concerning the long-term safety and efficacy of pharmacological management, which is associated with potential risks or side effects such as gastrointestinal bleeding, peptic ulcer disease, cardiovascular effects (due to NSAIDs), and overdose, misuse, or addiction (due to opioids) [4]. Potent analgesic medications that are well tolerated may help to avoid or delay surgical intervention.

Nerve growth factor (NGF) is a neurotrophin that regulates the structure and function of responsive sensory neurons, including small-diameter nociceptive afferents. It is recognized that NGF plays an important role in pain modulation via nociceptor sensitization [5,6]. Injury, inflammation, and chronic pain conditions are associated with the upregulation of NGF levels [7,8]. NGF levels also elevate in the joints of OA patients, suggesting that NGF also contributes to OA pain [9]. Tanezumab, a humanized IgG2 monoclonal antibody that selectively targets NGF, blocks the interaction of NGF with its receptors, the neurotrophic tropomyosin-related kinase A (trkA) receptor and the low-affinity NGF receptor p75(5). Several clinical randomized trials suggest that tanezumab is efficient in several distinct chronic pain conditions: interstitial cystitis [10], chronic low back pain [11], and OA [12,13].

Though prior studies established the superiority of tanezumab over placebo in the management of OA knee and hip pain, some reports describing the unexpected adverse events (AEs) initially described as osteonecrosis that required total joint replacement drove the US Food and Drug Administration (FDA) to impose a temporary partial clinical hold on tanezumab research for all indications except cancer pain on June 22, 2010. Until 2012, the FDA Arthritis Advisory Committee further endorsed clinical development of tanezumab by including additional measures to minimize risk and protect patient safety. To the best of our knowledge, there is no meta-analysis on the efficacy and safety of tanezumab on OA. Therefore, we performed a meta-analysis of all available randomized controlled trials (RCTs) to evaluate the efficacy and safety of tanezumab for treatment of OA knee and hip pain.

Methods

Search Strategy

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we conducted a comprehensive search of all relevant RCTs through PubMed, EBSCO, EMBASE, ScienceDirect, Web of Science, OVID, and Cochrane Library using the following terms: "tanezumab," "osteoarthritis," or "degenerative arthritis." All databases were searched from the available date of inception until the latest issue (January 2016). Only English publications were included. The references of retrieved articles were also examined to find other relevant articles.

Inclusion Criteria

The inclusion criteria were as follows: 1) study design: RCT; 2) study population: patients with OA of knee or hip; 3) intervention: tanezumab vs placebo or active comparator; 4) outcome measurement: mean change from baseline to end point in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, WOMAC physical functional, and patient's global assessment (PGA), discontinued due to AEs and serious AEs.

Patients included should be aged 18 years or older, have a body mass index of 39 kg/m^2 or lower, have a diagnosis of knee or hip OA based on the American College of Rheumatology criteria and radiographic confirmation (Kellgren-Lawrence grade $\geq$ 2, 0–4 scale), and be a candidate for invasive interventions such as intraarticular injections or total knee arthroplasty. Patients were also required to have a WOMAC pain subscale score in the index knee of 4 or higher (0–10 scale) at screening and 5 or higher at baseline, an increase of 1 or more after washout of prior analgesic treatment.

Patients were also excluded from the study if they were pregnant or intended to get pregnant during the study; or if they had any condition that could confound OA pain assessment, had rheumatoid arthritis, fibromyalgia, or other autoimmune disorders, or had significant cardiac, neurologic, or psychiatric conditions.

In individual studies, the patterns of efficacy (WOMAC pain subscale, WOMAC physical function subscale, and PGA) were obtained at baseline and at weeks 2, 4, 8, 16, 24, and even 32, or at early termination from the study. However, the mean baseline-to-end point changes of efficacy outcome measurement were used in this meta-analysis. For the event of inadequate pain relief, rescue medication was permitted, but it had to be discontinued at least 48 hours prior to any study visit.

Data Extraction

Two authors (J.Y. Chen and R.B. Li) independently extracted data (study characteristics, quality criteria, participant characteristics, intervention details, outcome measures, baseline and postintervention results) using a structured form. If there were several papers coming from the same study, only the most recent or complete study was included. Any disagreements about data extraction and quality assessment between the two reviewers were resolved by consensus, or, if necessary, by a third reviewer (Z.G. Zha).

Quality Assessment

All the studies were assessed independently using the Jadad five-point score for RCTs [14]. The Jadad score included method of randomization (0–2 points), double blinding (0–2 points), and description of withdrawals or dropouts (0–1 point). A study was assigned with 1) two points if it described the specific and appropriate method of randomization, 2) one point if the study was only described as randomized (only with terms such as "randomly," "random," or "randomization") without concrete method, and 3) zero if the study did not mention the randomization. The Jadad score was also applied to blinding. The maximum score that could be awarded to a trial was five points. Studies with a Jadad score of 3 points or higher were regarded as high quality.

Statistical Analysis

All statistical analyses were performed on Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) and STATA 12.0 (Stata Corp LP, College Station, TX, USA). The continuous data for meta-analysis were expressed as mean difference (MD) with 95% confidence interval (CI), while dichotomous data were presented as risk ratio (RR) with 95% CI. The heterogeneity across studies was estimated with chi-square test and the Higgins I^2 test. If heterogeneity was at a P value greater than 0.10 or an I^2 value of 50% or lower, a fixed-effects model was used; otherwise, a random-effects model was used. If a heterogeneity of I^2 value greater than 70% was evident, the inferior study was eliminated from the meta-analysis. The overall effect was tested using a Z-score with significance set at a P value of less than 0.05. Publication bias was visually assessed with funnel plots and quantitatively assessed using Egger's regression tests.

Results

Study Selection

Figure 1 shows the PRISMA flow diagram of study selection. Of the 750 articles initially identified, we retained 39 articles for screening after reviewing titles and abstracts based on the inclusion criteria. After reviewing full texts, we excluded 30 studies. Nine studies with

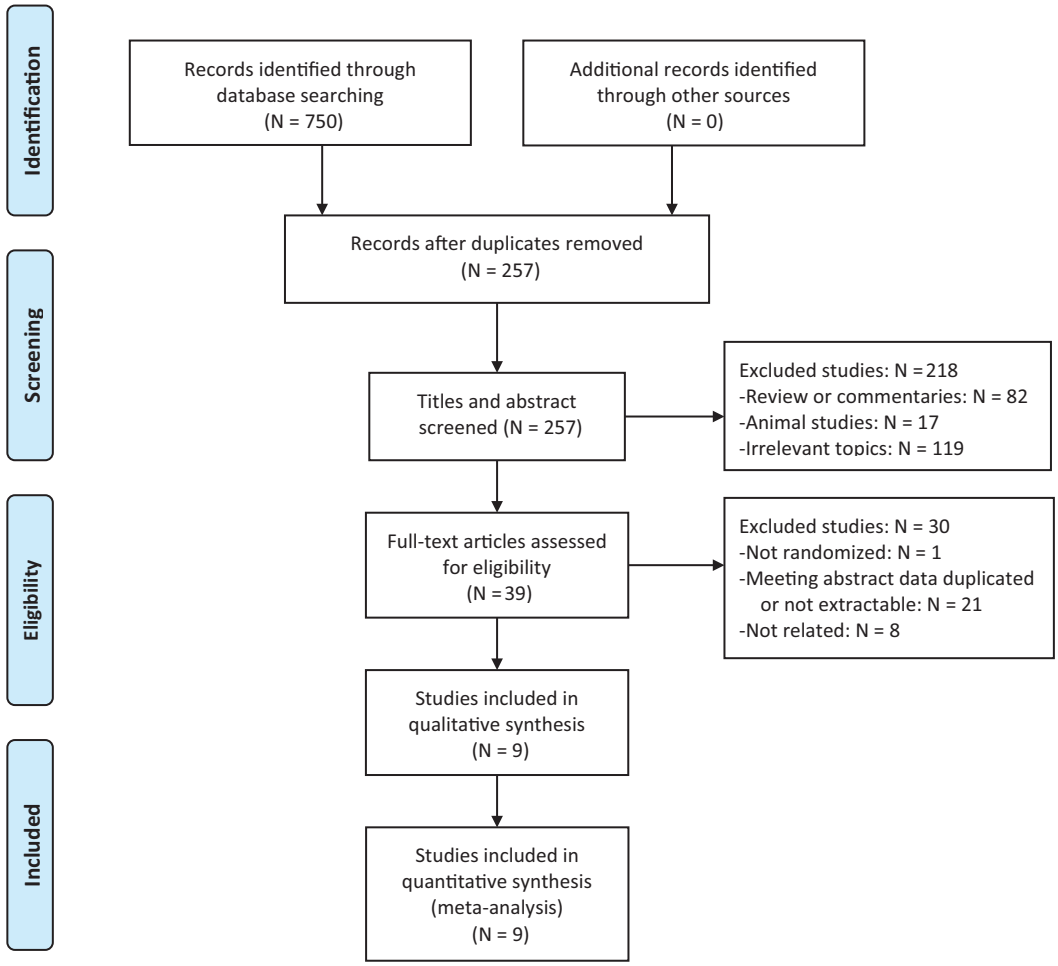

Figure 1 The PRISMA flow diagram of study selection.

7,665 individuals were included in the meta-analysis. The total sample size was based on the intent-to-treat (ITT) population.

Study Characteristics

The characteristics of the included studies are shown in Table 1, and details of the baseline patient characteristics are shown in Table 2. The nine included studies contain 10 RCTs (one study [13] contains two RCTs), which are all double-blind, parallel-group, placebo or active-controlled trials.

Most of the RCTs are phase III trials, and patients in the tanezumab dose receive 2.5/5/10 mg every eight weeks, while in two phase II trials [12,15] the tanezumab dose is 10–200 μg/kg. The pharmacokinetic/pharmacodynamic and dose-response analyses show that a dosing regimen adjusted for body weight provided negligible reduction in variability in systemic exposure over that predicted using a fixed-dose regimen [16]. As a result, the phase II and phase III data were pooled together. The doses of 10 and 25 μg/kg in phase II trials and 2.5 mg in phase III trials were combined as a low-dose subgroup; the doses of 50 μg/kg and 5 mg were combined as a moderate-dose subgroup; the doses of 100 and 200 μg/kg and 10 mg were combined as a high-dose subgroup. The efficacy data were analyzed in the low-dose, moderate-dose, and high-dose subgroups separately.

Balanescu et al. added tanezumab to oral diclofenac sustained release (DSR) in patients with hip or knee OA pain [17]. Ekman et al. compared intravenous tanezumab (5 or 10 mg) with placebo and naproxen (500 mg twice daily) [13], while another trial evaluated tanezumab monotherapy or combined with NSAIDs in the treatment of knee or hip OA pain [18].

Quality assessment of the included RCTs is presented in Table 3, with Jadad scores as well. All nine included studies were considered to be high quality, two studies were assessed as Jadad 3 point, three studies were assessed as Jadad 4 point, and four studies were assessed as Jadad 5 point. Publication bias was estimated via a funnel plot and a symmetric inverse funnel distribution was obtained. The Egger's regression tests also did not identify any evidence of publication bias among the included studies ($P = 0.658$).

Pain Intensity Reduction

All included RCTs evaluating the analgesic efficacy utilize WOMAC pain reduction as the primary or secondary outcome. The mean baseline-to-end point changes of WOMAC pain are summarized in Figure 2. All WOMAC pain scores were assessed using a numerical rating scale of 0–10, in which a decreasing score represents a reduction in pain intensity. WOMAC pain scores assessed on a 0–100 mm visual analogue scale in two RCTs [12,15] were converted to this numerical rating scale for analysis. The pain intensity reductions are significantly different between tanezumab-treated and placebo-treated patients (5,879 patients, MD = -0.98, 95% CI = -1.18– -0.79, $P < 0.00001$) (Figure 2), suggesting tanezumab treatment is favorable for pain intensity reduction. These studies show a mild degree of heterogeneity ($P = 0.40$, $I^2 = 5\%$).

Functional Improvement

All included trials provide specific relevant data for comprehensive analysis of WOMAC physical function. All WOMAC physical function scores were assessed using the numerical rating scale of 0–10, in which a lower score indicates less limitation of physical function.

Table 1 Characteristics of included studies

Study	Design	Country	Patients, No.	Index joint	Treatment period, wk	Coprimary end points
Balanescu 2014	RCT	Rumania	607	Knee and hip	24	WOMAC pain, WOMAC physical function, PGA
Brown 2012	RCT	America	697	Knee	32	WOMAC pain, WOMAC physical function, PGA
Brown 2013	RCT	America	627	Hip	32	WOMAC pain, WOMAC physical function, PGA
Brown 2014	RCT	America	219	Knee and hip	32	Nerve conduction attributes, heart rate variability with deep breathing
Ekman 2014A	RCT	America	828	Knee	24	WOMAC pain, WOMAC physical function, PGA
Ekman 2014B	RCT	America	840	Knee and hip	24	WOMAC pain, WOMAC physical function, PGA
Lane 2010	RCT	America	450	Knee	26	Knee pain while walking, PGA of response to therapy
Nagashima 2011	RCT	Japan	83	Knee	13-17	Index knee pain intensity, WOMAC subscales
Schnitzer 2015	RCT	America	2,700	Knee and hip	16	WOMAC pain, WOMAC physical function, PGA
Spierings 2013	RCT	America	614	Knee and hip	16	WOMAC pain

PGA = patient's global assessment; RCT = randomized controlled trial; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2 Baseline patient characteristics

Study	Group	N	Female gender, %	Age, y	Kellgren-Lawrence grade, %			Duration since diagnosis, y
					2	3	4	
Balanescu 2014	Tan 2.5 mg + DSR 75 mg	157	77.1	62.1	49.0	43.3	7.6	6.1
	Tan 5mg + DSR 75 mg	150	73.3	62.2	42.7	47.3	10.0	6.7
	Tan 10 mg + DSR 75 mg	145	82.8	63.1	50.3	42.8	6.9	6.6
	Placebo + DSR 75 mg	152	77.6	62.3	44.7	44.7	10.5	6.1
Brown 2012	Tan 2.5 mg	172	54.7	60.8	37.2	43.0	18.0	7.3
	Tan 5 mg	172	58.7	62.1	37.2	51.7	10.5	7.5
	Tan 10 mg	174	60.9	61.4	40.8	44.3	14.9	9.5
	Placebo	172	69.2	62.2	39.5	47.7	12.8	8.2
Brown 2013	Tan 2.5 mg	155	65.2	62.4	45.8	34.2	20.0	6.0
	Tan 5 mg	154	59.7	61.8	46.8	35.1	17.5	6.3
	Tan 10 mg	157	56.1	61.8	42.7	36.9	20.4	5.6
	Placebo	155	66.5	61.9	47.1	36.1	16.8	5.6
Brown 2014	Tan 5 mg	73	60.3	57.8	34.2	24.7	15.1	NA
	Tan 10 mg	74	63.5	58.0	29.7	35.1	13.5	NA
	Placebo	72	54.2	56.3	43.1	27.8	11.1	NA
Ekman 2014 A	Tan 5 mg	206	59.2	61.1	36.9	52.4	10.7	7.9
	Tan 10 mg	208	61.5	61.1	47.1	43.3	9.6	8.5
	Naproxen 500 mg	206	62.6	61.4	48.1	43.2	8.7	7.2
	Placebo	208	57.7	60.9	42.8	43.8	13.5	9.2
Ekman 2014 B	Tan 5 mg	211	63.5	59.8	49.3	36.5	14.2	6.4
	Tan 10 mg	209	61.2	59.2	48.3	34.4	17.2	6.8
	Naproxen 500 mg	211	61.2	60.3	48.3	39.8	8.1	7.7
	Placebo	209	65.1	60.1	51.2	37.8	10.5	6.3
Lane 2010	Tan 10 μg/kg	74	66.2	58.3	28.8	71.2*		NA
	Tan 25 μg/kg	74	67.6	59.9	31.1	68.9*		NA
	Tan 50 μg/kg	74	50.0	60.4	39.2	60.8*		NA
	Tan 100 μg/kg	74	69.5	57.1	29.7	69.3*		NA
	Tan 200 μg/kg	74	54.1	58.4	26.0	74.0*		NA
	Placebo	74	56.8	58.1	24.7	75.3*		NA
Nagashima 2011	Tan 10 μg/kg	15	66.7	59.3	46.7	53.3	0	4.5
	Tan 25 μg/kg	15	53.3	57.3	60.0	40.0	0	7.3
	Tan 50 μg/kg	15	73.3	60.7	93.3	6.7	0	4.2
	Tan 100 μg/kg	16	75.0	58.1	68.8	31.3	0	3.8
	Tan 200 μg/kg	6	83.3	60.0	50.0	50.0	0	5.4
	Placebo	16	68.8	59.4	50.0	43.8	6.3	7.9
Schnitzer 2015	Tan 5 mg	541	72.5	61.9	33.5	35.3	31.2	7.3
	Tan 10 mg	542	72.3	62.0	34.5	37.5	28.0	7.1
	Tan 5 mg + NSAID†	536	67.7	61.7	34.2	39.6	26.0	7.0
	Tan 10 mg + NSAID†	542	68.1	61.3	29.7	40.2	30.1	7.4
	Placebo + NSAID†	539	72.0	61.3	36.5	40.3	23.2	7.5
Spierings 2013	Tan 5 mg	161	59.6	57.8	48.4	37.3	14.3	7.6
	Tan 10 mg	150	62.7	57.0	48.7	36.7	14.7	7.5
	Oxycodone 10–40 mg	158	62.7	57.6	50.6	34.8	14.6	6.2
	Placebo	141	65.2	57.2	47.5	39.7	12.8	7.4

DSR = diclofenac sustained release; NA = data not available; Tan = tanezumab.
*Kellgren-Lawrence grade 3 or 4.
†Naproxen 500 mg or celecoxib 100 mg.

The WOMAC physical function scores are significantly different between the tanezumab-treated and placebo-treated patients (6,078 patients, MD = -1.10, 95% CI = -1.28– -0.92, $P < 0.00001$) (Figure 3). These studies show a mild degree of heterogeneity ($P = 0.25$, $I^2 = 15\%$).

Table 3 Quality assessment of included RCTs

Study	Randomization	Double-blinding	Withdrawals and dropouts	Jadad score
Balanescu 2014	2	2	1	5
Brown 2012	1	2	1	4
Brown 2013	1	1	1	3
Brown 2014	2	2	1	5
Ekman 2014 A/B	1	1	1	3
Lane 2010	2	2	1	5
Nagashima 2011	2	2	1	5
Schnitzer 2015	2	1	1	4
Spierings 2013	1	2	1	4

RCT = randomized controlled trial.

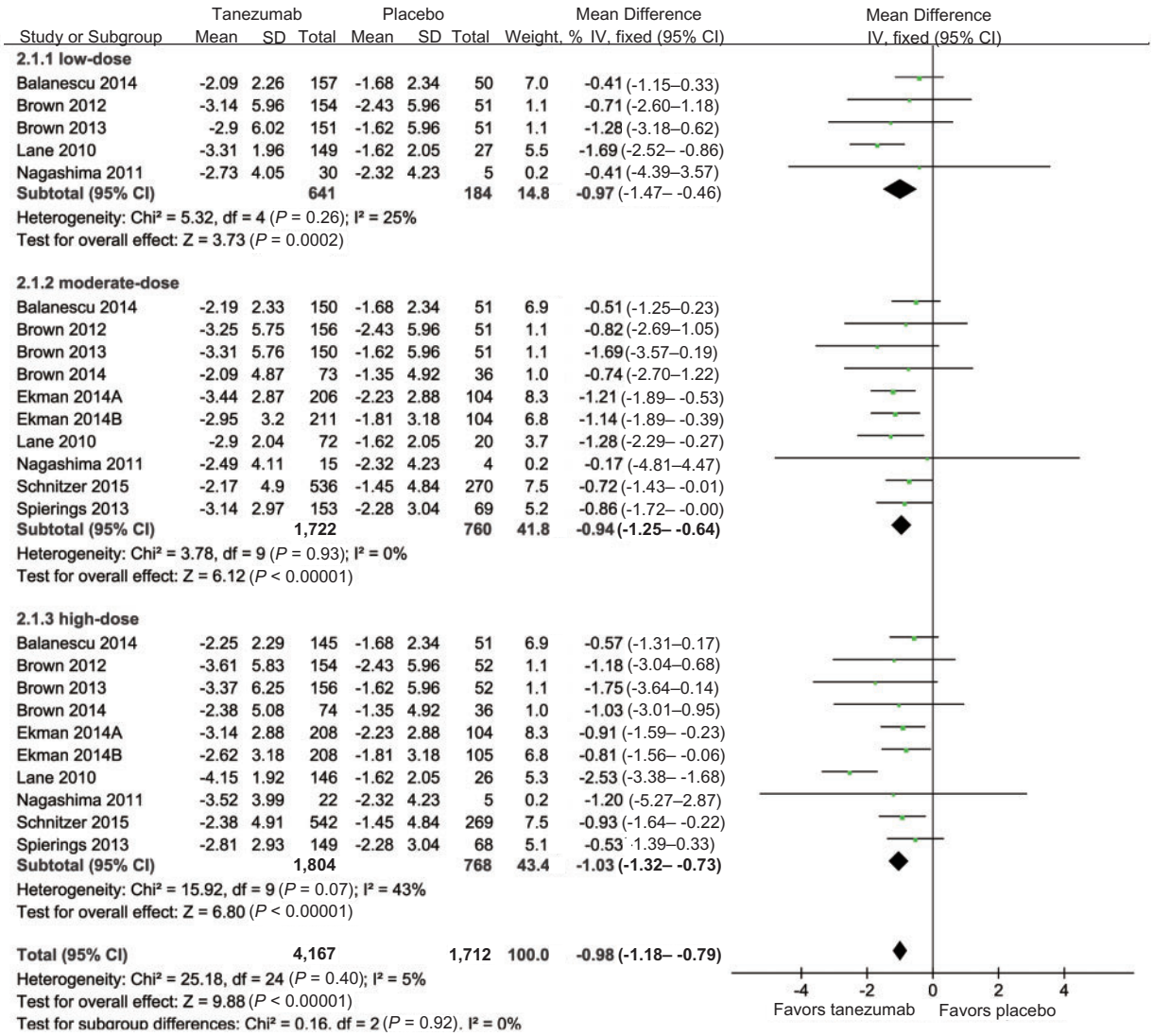

Figure 2 Forest plots of mean baseline-to-end point change in Western Ontario and McMaster Universities Osteoarthritis Index pain after tanezumab treatment vs placebo (mean ± SD).

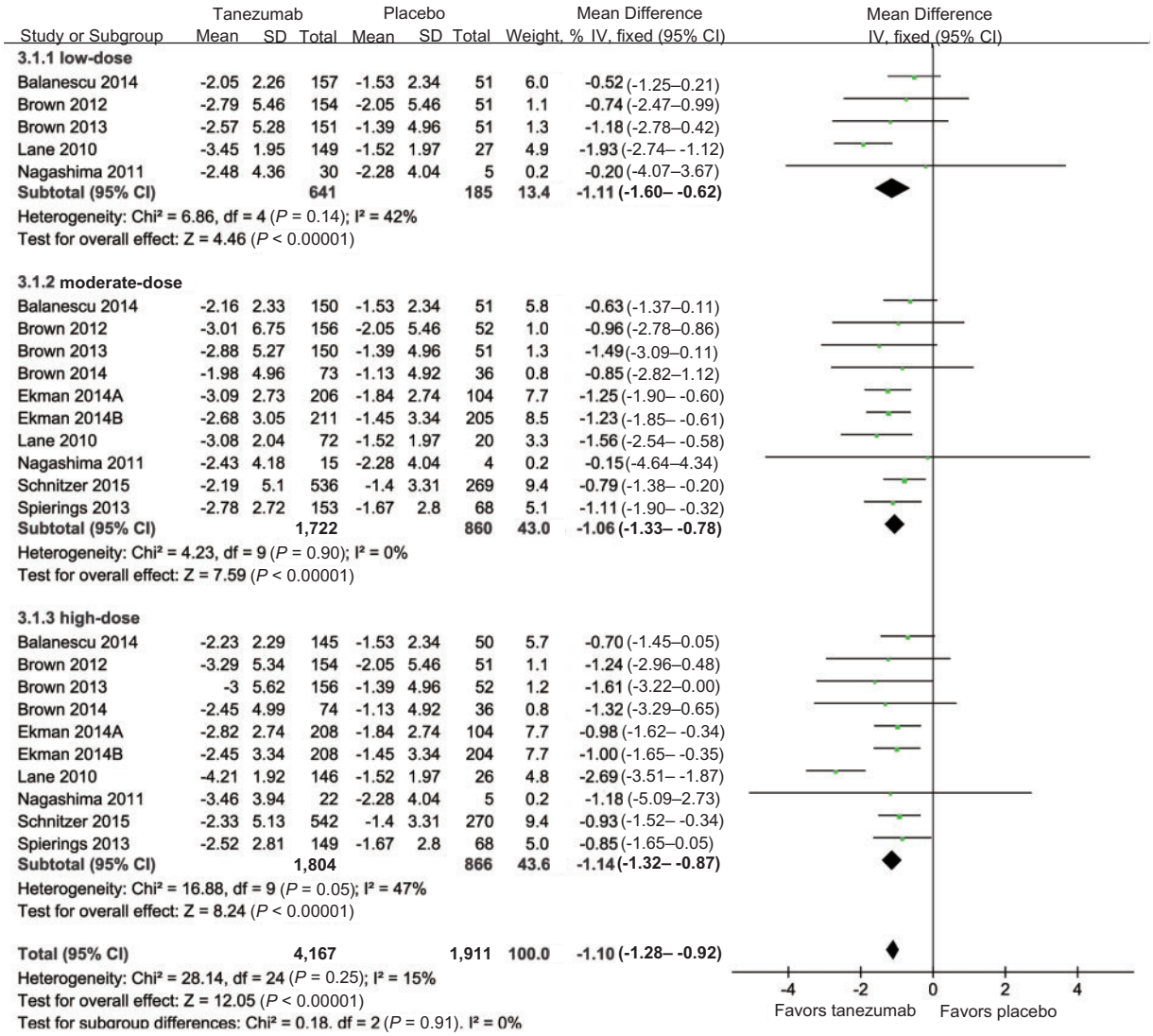

Figure 3 Forest plots of mean baseline-to-end point change in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function after tanezumab treatment vs placebo (mean ± SD).

Patient's Global Assessment

Nine of the 10 trials report data of patient's global assessment (PGA). PGA of OA was assessed using a five-point Likert scale (where 1 = very good and 5 = very poor). The reduction of PGA scores is significantly larger in the tanezumab-treated vs placebo-treated patients (5,366 patients, MD = -0.27, 95% CI = -0.34– -0.20, $P < 0.00001$) (Figure 4). No significant heterogeneity was observed between studies ($P = 0.99$, $I^2 = 0\%$).

Safety

All included RCTs provide specific data for comprehensive analysis of discontinuity due to AEs and serious AEs. Serious AEs were defined as adverse events such as life-threatening or disabling events resulting in hospitalization or death or resulting in a congenital anomaly or birth defect. The number of discontinued patients due to AEs is significantly larger after tanezumab vs placebo treatment (6,537 patients, RR = 1.62, 95% CI = 1.29–2.03, $P < 0.0001$) (Figure 5). However, the occurrence rates of serious AEs is not significantly different between tanezumab-treated and placebo-treated patients (7,481 patients, RR = 1.19, 95% CI = 0.94–1.52, $P = 0.15$) (Figure 6). The most frequent AEs reported in 10 trials are summarized in Table 4. Tanezumab-treated patients suffered significantly more paraesthesia, arthralgia, hypoaesthesia, and peripheral edema. In total, 10 deaths were reported in five studies [13,17–20], but none of the deaths was considered by investigators to be related to medication.

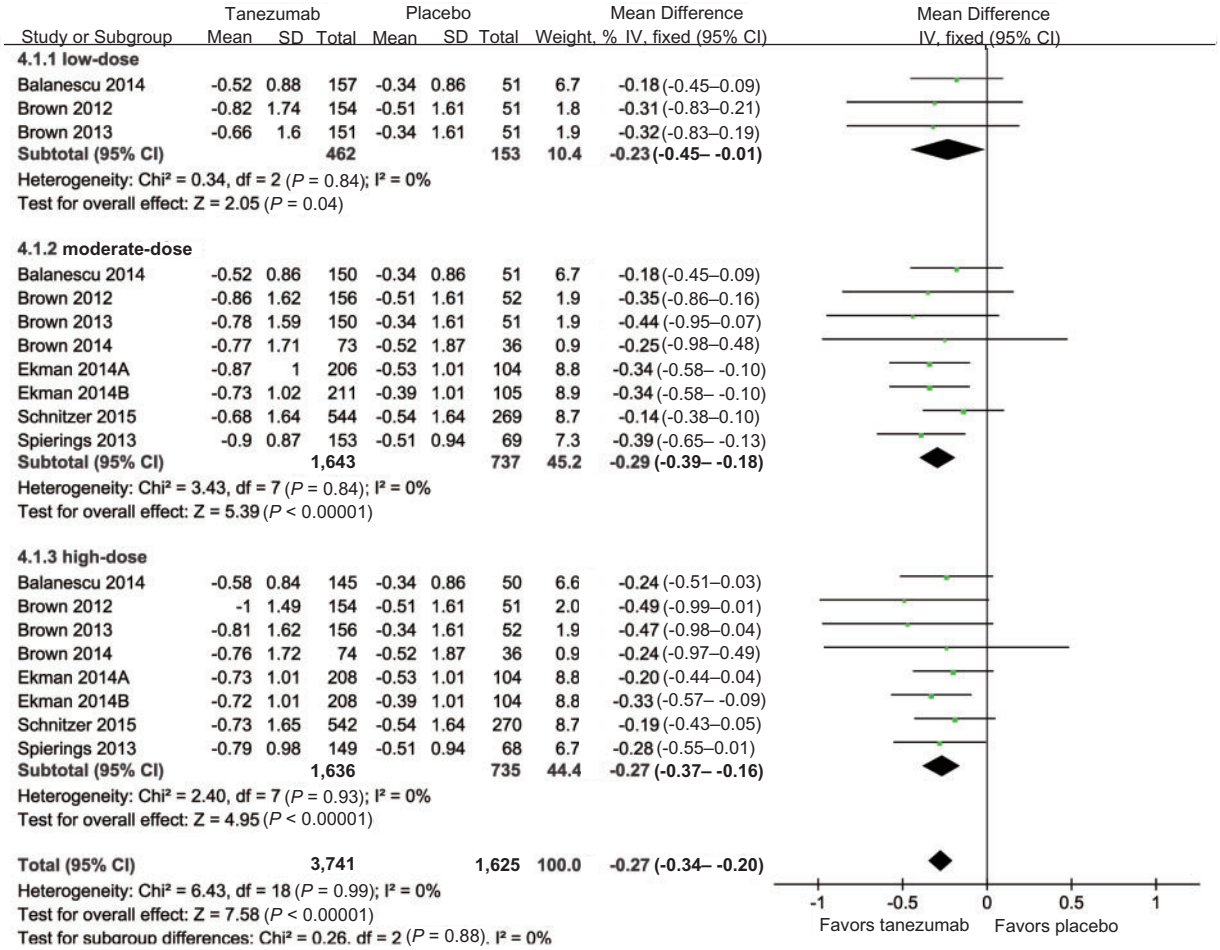

Figure 4 Forest plots of mean baseline-to-end point change in patient's global assessment (PGA) after tanezumab treatment vs placebo (mean ± SD).

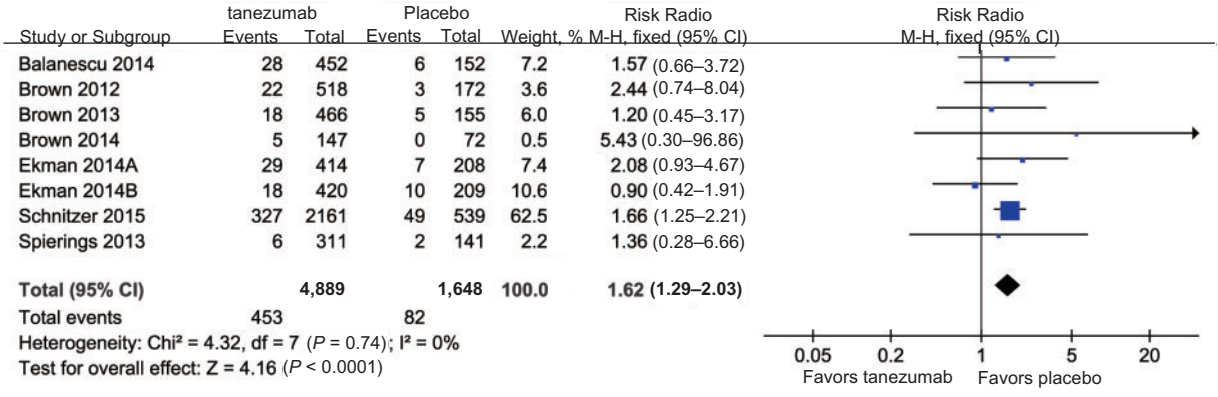

Figure 5 Forest plots: number of discontinuities due to adverse events after tanezumab treatment vs placebo.

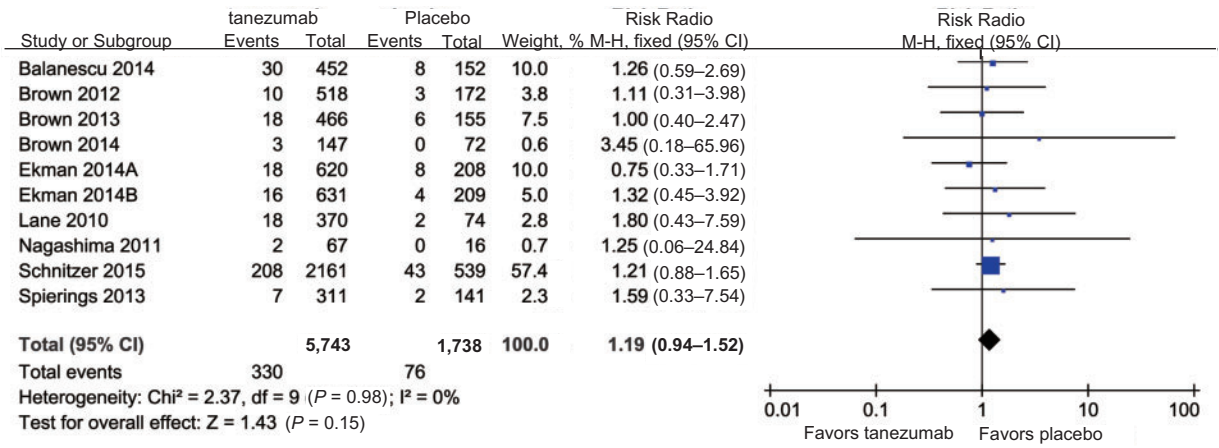

Figure 6 Forest plots: number of serious adverse events after tanezumab treatment vs placebo.

Table 4 Meta-analysis of most frequent adverse events after tanezumab or placebo treatment in OA patients

Adverse event	No. of included studies	Patients with AEs/total		RR (95% CI)	*P*	$P_{heterogeneity}$
		Tanezumab	Placebo			
Paraesthesia	10	356/5,901	40/1,738	2.55 (1.85–3.51)	<0.00001	0.80
Headache	10	261/5,901	80/1,738	0.94 (0.73–1.20)	0.60	0.40
Arthralgia	9	494/5,834	88/1,722	1.59 (1.28–1.98)	<0.0001	0.53
Hypoaesthesia	9	229/5,834	24/1,722	2.55 (1.70–3.83)	<0.00001	0.86
Hyperesthesia	8	33/3,673	1/1,183	2.49 (0.93–6.66)	0.07	0.99
Peripheral edema	7	272/5,218	20/1,509	3.65 (2.35–5.68)	<0.00001	0.72
Peripheral neuropathy	7	16/3,303	1/1,109	1.64 (0.56–4.81)	0.37	1.00
Upper respiratory tract infection	7	214/4,913	56/1,429	1.08 (0.81–1.44)	0.61	0.08
Urinary tract infection	6	189/4,848	47/1,435	1.14 (0.83–1.56)	0.41	0.43

AE = adverse event; CI = confidence interval; OA = osteoarthritis; RR = risk ratio.

Sensitivity Analyses

In order to explore the impact of a single study on the main outcomes, we performed a "one study removed" analysis by re-estimating the meta-analysis after removing one study at a time for each main outcome. Sensitivity analysis showed that heterogeneity in low-dose and high-dose groups for WOMAC pain and physical function were decreased greatly by removing Lane et al. [12], but the pooled result was unchanged. One reason for this is that the tanezumab dose in Lane et al. [12] was dependent upon weight. In this meta-analysis, the doses of 10 and 25 μg/kg and 2.5 mg were combined as a low-dose subgroup, while the doses of 100 and 200 μg/kg and 10 mg were combined as a high-dose subgroup.

Discussion

The analgesic efficacy of tanezumab, a humanized monoclonal antibody, is concerned with its ability to block NGF by interacting with its receptors TrkA and p75 in the peripheral nervous system. Previous preclinical studies indicate that tanezumab or its murine precursor can reduce pain intensity in a mouse model of bone cancer pain and fracture pain [21] and in a rat model of inflammatory arthritis pain [22].

The efficacy of tanezumab as an analgesic for OA knee and hip pains was evaluated in 10 placebo-controlled RCTs involving 7,665 patients. Tanezumab treatment at all three doses was superior to placebo treatment at all three coprimary endpoints, including measures of reduction in pain intensity, function improvement, and PGA of OA. In individual studies, higher doses tanezumab apparently have greater efficacy but are also associated with a higher likelihood of AEs [19,20]. However, we found that the magnitudes of effect are generally similar for low-, moderate-, and high-dose tanezumab vs placebo across all three coprimary endpoints. The low doses tanezumab (10 and 25 μg/kg and 2.5 mg) provide similar effectiveness in reducing pain and

improving function and are associated with fewer AEs. Specifically, significant and rapid improvement in pain was observed among tanezumab-treated patients after one week and remained significant throughout the remainder of the study [12,23].

As reported, tanezumab vs oxycodone provides significant improvement in WOMAC pain, physical function, and PGA of OA at week 8, with fewer AEs [23]. After comparing efficacy and long-term safety of tanezumab with naproxen and celecoxib, Ekmans et al. and Schnitzer et al. found that subjects receiving partial symptomatic relief of OA pain with NSAIDs may benefit more from tanezumab monotherapy [13,18]. According to a long-term open-label study, repeated tanezumab injections (administered at an eight-week interval and up to a total of eight infusions) in patients with moderate-to-severe knee OA provide continued pain relief and functional improvement with a low incidence of side effects [24]. A systematic review demonstrates that treatment with anti-NGF antibodies (including tanezumab, fulranumab, and fasinumab) provides efficacy in OA of knee and hip pain, and lower doses of tanezumab (2.5 and 5 mg) are associated with fewer AEs leading to study withdrawal, compared with the 10 mg dose, without significant difference in efficacy [25].

Overall, the rates of discontinuation due to AEs and serious AEs after tanezumab treatment are low, indicating that tanezumab is safe and generally well tolerated. Meta-analysis shows that tanezumab-treated patients suffered significantly more paraesthesia, arthralgia, hypoaesthesia, and peripheral edema. The majority of AEs reported by tanezumab-treated patients, including abnormal peripheral sensations, are mild to moderate in severity and transitory without persistent changes in neurological examinations, and most resolve before study completion [12,23]. The IgG used to inhibit NGF is not expected to cross the blood-brain barrier under normal circumstances, making it unlikely that there would be AEs due to anti-NGF in the central nervous system [26]. In clinical study, there were no significant differences in memory function by HVLT-R between tanezumab and placebo groups, and the AEs of abnormal peripheral sensation also suggest that the effects of tanezumab are limited to the peripheral nervous system. The incidences of most neurologic AEs occurred with the first dose of tanezumab but were rarely observed with subsequent doses, except hypoesthesia and paresthesia, which occurred at different time points and were not predictable [19]. One study focused on nerve safety of tanezumab indicates that 5 or 10 mg tanezumab every eight weeks is not associated with structural neurotoxic effects on large motor or sensory nerves, autonomic nerves, or cutaneous small sensory fibers when used to treat chronic pain in individuals without known peripheral neuropathy [27]. Moreover, no significant differences were identified in blood, urine, electrocardiogram, blood pressure assessments, or other laboratory. Tanezumab treatment does not seem to adversely affect gastrointestinal, cardiovascular, liver, or kidney function [13,18].

It should be mentioned that the FDA imposed a partial clinical hold on noncancer pain-related tanezumab studies due to unexpected AEs initially reported as osteonecrosis that required total joint replacement from June 2010 to August 2012. A blinded adjudication committee reviewed events in 249 patients with an investigator-reported adverse events of osteonecrosis and/or total joint replacements (TJRs). Only two events were adjudicated as primary osteonecrosis, while 68 events were adjudicated as rapid progression of OA (RPOA) [28]. Tanezumab treatment did not increase the risk of osteonecrosis but was associated with an increase in RPOA. Time to event analysis of RPOA in the phase III tanezumab studies depicted that RPOA was related to the dose of tanezumab administered as monotherapy; combination treatment of 10 mg tanezumab with an NSAID was associated with the highest estimated rate of RPOA. The risk factors for rapid progression of OA include higher doses of tanezumab ($\geq$10 mg), tanezumab combined with NSAIDs, and preexisting subchondral insufficiency fractures [28,29]. Although addition of tanezumab to stable NSAIDs provides clinically meaningful and significant improvements in OA pains, further investigations of tanezumab monotherapy for OA pain treatment are required.

In this meta-analysis, we found that tanezumab vs placebo provides superior pain relief and improvement in physical function in osteoarthritis patients, with acceptable AEs. The low doses of tanezumab provide similar effect and lead to fewer AEs compared with moderate and high doses. As we found that tanezumab is efficacious and safe, this work can be an important reference to policy-making. For example, the addition of the drug to the relevant guidelines as a first-line treatment for OA may be considered.

The 10 included RCTs are all double-blind and high quality (Figure 3). The results of these analyses may be scientifically and clinically important. However, this meta-analysis has several limitations. First, the search strategy does not cover unpublished trials, which might result in selection bias as trials with positive results are more likely to be included. Second, the language is restricted to English, so trials reported in other languages may be missed. Third, all included trials were sponsored by pharmaceutical companies, but this is a known potential source of bias.

Conclusions

Tanezumab vs placebo provides superior pain relief and improvement in physical function and patient's global assessment in knee and hip osteoarthritis patients and is generally well tolerated with acceptable adverse events, such as paraesthesia, arthralgia, hypoaesthesia, and peripheral edema. Low-dose tanezumab (10 and 25μg/kg and 2.5 mg) provides similar effectiveness in reducing pain

and improving function and is associated with fewer AEs. The long-term safety of tanezumab on osteoarthritis knee and hip pain needs further investigation.

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