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Targeting Nerve Growth Factor for Pain Management in Osteoarthritis—Clinical Efficacy and Safety

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KEYWORDS

• NGF • Anti-NGF • Osteoarthritis • Pain • Nerve growth factor • Review

KEY POINTS

- Nerve growth factor plays a key role in pain hypersensitization in osteoarthritis.
- Inhibition of nerve growth factor is effective at reducing pain and improving physical function from osteoarthritis of the hip or knee.
- Use of these agents is complicated by adverse joint safety events, notably rapidly progressive osteoarthritis and an increased need for joint replacements.
- The mechanism driving these joint safety events remains poorly understood and is an important area for further study.

BACKGROUND

Osteoarthritis (OA) is a leading cause of global disability,¹ affecting as many as 250 million people worldwide.² Estimates of the direct and indirect economic costs of OA range from 1% to 2.5% of the gross domestic product in the United States, Canada, France, the United Kingdom, and Australia.³ Guidelines for management of OA generally agree on nonpharmacologic management with exercise, weight loss, education and self-management, and hip or knee joint replacement in appropriate patients. Pharmacologic agents that are variably recommended for management of OA include

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acetaminophen, topical and oral nonsteroidal anti-inflammatory drugs (NSAIDs), duloxetine, tramadol, and intra-articular corticosteroids.⁴ Due to concerns regarding limited and/or uncertain efficacy^{5,6} and overall safety of many of these agents, their utility in OA management is limited. Nontramadol opioid medications have serious safety issues, may be less effective than nonopioids in OA, and generally are not recommended.⁷ Given this significant unmet need for novel therapeutics, the development of additional effective nonopioid pain medications for OA and other conditions has been a topic of intense investigation, including compounds targeting nerve growth factor (NGF). The clinical efficacy and safety profile of these anti-NGF agents are the focus of this review.

BIOLOGIC ROLE OF NERVE GROWTH FACTOR

NGF is a member of a family of proteins called neurotrophins that regulate the development and survival of certain neurons. NGF is critical to the development of the peripheral sensory and sympathetic nervous system in mammals,^{8,9} including humans.¹⁰ NGF mediates its effects on the nervous system via signaling through 2 receptors: a specific tyrosine receptor kinase A (TrkA) (Fig. 1) and the low-affinity p75 neurotrophin receptor.¹¹ Humans with mutated NGF-B genes have congenital pain insensitivity,¹⁰ and mutations in TrkA cause pain insensitivity, anhidrosis, and developmental delay.¹²

Aside from its profound developmental importance, NGF plays a role in pain signaling in adults. Injection of NGF induces hyperalgesic effects including heat sensitivity, myalgias and tenderness to palpation lasting weeks, and NGF expression has been associated with inflammatory, neuropathic, visceral, and cancer pain.¹³ NGF is released by inflammatory cells in response to injury,¹⁴ and appears to play an important role in pain and cachexia in pre-clinical models of inflammatory arthritis.¹⁵ NGF also regulates levels of neuropeptides such as substance P and calcitonin gene-related peptide in adult sensory neurons.¹⁶ NGF binding its TrkA receptor leads hypersensitization via several mechanisms, including rapid post-translational modifications

Fig. 1. Anti-NGF antibodies inhibit NGF-TrkA binding. The anti-NGF monoclonal antibodies tanezumab, fasinumab, and fulranumab bind to NGF and inhibit NGF interaction with its high-affinity receptor TrkA. The p75 receptor (not shown) is a low-affinity receptor that interacts with NGF. The p75 receptor can enhance NGF-TrkA interactions, although the precise interactions between TrkA and p75 are incompletely understood. Ab, antibody.

of ion channels, and increasing expression of a host of receptors in the membranes of sensory neurons.¹⁷ A model of the effects of NGF on pain signaling is depicted in **Fig. 2**. NGF binds to TrkA, and the complex is endocytosed and retrogradely transported to neuronal cell bodies, where it modulates the expression of cell surface receptors involved in nociception in the dorsal root ganglion, thus initiating peripheral sensitization and pain hypersensitivity.^{18,19}

NGF has effects beyond the nervous system. NGF-TrkA signaling in sensory nerves during late embryogenesis is required for normal vascularization and ossification of endochondral bone.²⁰ Sensory nerves emanating from the dorsal root ganglia extensively innervate the surfaces of mammalian bone. NGF/TrkA signaling in skeletal sensory nerves has been shown to be an early response to mechanical loading of bone. In vivo mechanical loading in mice and in vitro mechanical stretch were shown to induce profound up-regulation of NGF in osteoblasts. Elimination of TrkA signaling in mice was found to greatly attenuate load-induced bone formation whereas administration of exogenous NGF was found to significantly increase load-induced bone formation.²¹

Studies in mice and humans have suggested that there is a localized increase in NGF at sites of inflammation.²² Human osteoarthritic chondrocytes in vitro demonstrate increased expression of TrkA and NGF- β protein relative to nonosteoarthritic chondrocytes, and the degree of expression increased with worsening osteoarthritic damage.²³ NGF is detectable in the synovial fluid of human patients with rheumatoid arthritis and OA but not in controls.²⁴ In different models of inflammation, NGF has

Fig. 2. NGF initiation of pain hypersensitization. NGF is released by damaged tissues and binds to its specific receptor, TrkA, on the terminals of sensory nociceptive neurons. The endocytosed NGF-TrkA complex is transported retrograde to the neuronal cell body in the dorsal root ganglion, where it increases expression of ion channels and neuropeptides, such as substance P and calcitonin gene-related peptide (CGRP), leading to peripheral and central pain hypersensitization. CNS, central nervous system.

been suggested to down-regulate tissue inflammation, including down-regulation of inflammatory cytokine production and up-regulation of the anti-inflammatory cytokine interleukin 10; thus, NGF may serve in part to dampen inflammatory responses to facilitate restoration of homeostasis.

NGF and its receptor, TrkA, appear also to regulate bone cells, including osteoblast²⁵ and osteoclast differentiation²⁶ and osteocyte activity²⁷ as well as homeostasis articular chondrocytes.²⁸ The role of neurotrophins on the differentiation and function of bone cells is an important area for further research, as better knowledge of this relationship and the interactions between bone cells, inflammatory cells, and sensory neurons is critical to understanding both the mechanism of action and the important adverse effects of anti-NGF agents.

NGF inhibitors in advanced phases of development for OA include tanezumab, a recombinant humanized anti-NGF monoclonal antibody,²⁹ and fasinumab, a recombinant fully human anti-NGF monoclonal antibody (**Table 1**).³⁰ Fulranumab, another human anti-NGF monoclonal antibody,³¹ is discussed in later but is no longer in active development for OA.³² These agents block the interaction of NGF with its receptors, TrkA and p75 (see **Fig. 1**).²⁹ Small-molecule selective TrkA inhibitors also are in development for OA pain³³ but have no published phase III data thus are not included in this review.

CLINICAL OUTCOMES IN ANTI-NERVE GROWTH FACTOR TRIALS

Many clinical trials of anti-NGF agents for hip and knee OA use scores on the Western Ontario and McMaster Universities Arthritis Index (WOMAC) as outcomes. The WOMAC is a self-administered patient-reported outcome instrument for OA of the hip or knee. It consists of 3 subscales (pain, stiffness, and physical function) covering 24 total items.³⁴ There are multiple versions of WOMAC and multiple scoring scales, including a 5-level Likert scale, 0 to 10 numeric rating scale (NRS), and 0 to 100 visual analog scale (VAS), leading to widely varying ranges of possible scores depending on the scale used and whether a total or average score is reported.³⁵ Least squares (LS) mean difference often is reported, which is the difference of group means after having adjusted for covariate(s). Whenever possible, the scale used in the referenced study are discussed.

EARLY-PHASE TRIALS OF ANTI-NERVE GROWTH FACTOR AGENTS FOR HIP OR KNEE OSTEOARTHRITIS

The initial studies of anti-NGF agents for OA of the hip or knee used intravenous (IV) formulations of tanezumab or fulranumab, each humanized anti-NGF antibodies, either alone or in combination with NSAIDs. In an early proof-of-concept study of tanezumab, 450 individuals with knee OA were randomized to receive IV tanezumab at various doses ranging from 10 $\mu\text{g/kg}$ to 200 $\mu\text{g/kg}$ for 2 administrations 8 weeks apart, compared with placebo. Averaged over 16 weeks, participants receiving tanezumab had reductions in WOMAC Pain score of 46% to 64% versus 23% for placebo, and reductions (indicating improvement) in the WOMAC Physical Function score of 47% to 65% versus 22% for placebo. Adverse events were common, especially at higher doses of tanezumab, 100 $\mu\text{g/kg}$ and above, including headache, upper respiratory tract infection, and paresthesias.³⁶ A smaller phase II trial of 83 Japanese individuals with moderate to severe knee OA received a either single dose of IV tanezumab at doses ranging from 10 $\mu\text{g/kg}$ to 200 $\mu\text{g/kg}$ or placebo. At week 8, those receiving tanezumab, 25 $\mu\text{g/kg}$, 100 $\mu\text{g/kg}$, or 200 $\mu\text{g/kg}$, had improvement in WOMAC scores for pain (100-mm VAS; LS mean differences from placebo of -11.5 , -9.6 , -18.8 ,

Table 1
Summary of phase III trials of anti-nerve growth factor agents after lifting of Food and Drug Administration hold in 2015

Trial	Intervention	Follow-up	Results	Joint Adverse Events
Schnitzer et al, ⁵⁵ 2019: TNZ for OA	698 patients randomized to TNZ, 2.5 mg, d 1; TNZ, 2.5 mg, wk 8; TNZ, 2.5 mg, d 1; TNZ, 5 mg, wk 8; or to PBO	40 wk	Both TNZ doses improved WOMAC Pain and Physical Function subscores and improved PGA-OA compared with PBO at 16 wk.	RPOA in 2.2% of TNZ, 2.5 mg/2.5 mg; 0.4% of TNZ, 2.5 mg/5 mg; 0% of PBO. TJR in 3.5% of TNZ, 2.5 mg/2.5 mg; 6.7% of TNZ, 2.5 mg/5 mg; 1.7% of PBO
Berenbaum et al, ⁵⁶ 2020: TNZ for OA	849 patients randomized to TNZ, 2.5 mg; TNZ, 5 mg; or PBO, every 8 wk for 3 doses	48 wk	Both TNZ doses improved WOMAC Pain and Physical Function subscores compared with PBO at 24 wk. Only TNZ, 5 mg, was superior to PBO for PGA-OA at 24 wk.	RPOA in 1.4% of TNZ 2.5, mg; 2.8% of TNZ, 5 mg; 0% of PBO. TJR in 7.8% of TNZ, 2.5 mg; 7.0% TNZ, 5 mg; 6.7% PBO
Hochberg et al, ⁵⁸ 2019: TNZ for OA	2996 patients randomized to TNZ, 2.5 mg, or TNZ, 5 mg, every 8 wk; or oral NSAID, up to wk 56	80 wk	TNZ, 5-mg dose, improved WOMAC Pain and WOMAC Physical Function at 16 wk compared with NSAIDs but no difference from NSAIDs at 56 wk. TNZ, 2.5 mg, not statistically different from NSAIDs at 16 wk or 56 wk	Composite joint safety outcome 3.8%, TNZ, 2.5 mg; 7.1%, TNZ 5 mg; 1.5% NSAIDs
Dakin et al, ⁵⁹ 2019: FAS for OA	421 patients randomized to FAS, 1mg, 3mg, 6mg, or 9mg; or to PBO every 4 wk for 4 doses	36 wk	All FAS doses improved WOMAC Pain and Physical Function subscores compared with PBO at 16 wk. Only FAS, 1 mg and 9 mg, improved PGA-OA compared with PBO at 16 wk.	RPOA in 5% of fasinumab group (all doses averaged), 0% PBO. Subchondral insufficiency fracture in 1.8% fasinumab, 1.2% PBO. TJR 4% in both fasinumab and PBO
Markman et al, ⁶² 2020: TNZ for LBP	1832 patients randomized to TNZ, 5-mg SC; TNZ 10-mg SC; TRA; or PBO every 8 wk, up to wk 56	80 wk	TNZ, 10-mg dose, improved LBPI and RDQ score compared with PBO, and improved RDQ compared with TRA at 16 wk. TNZ, 5-mg dose, not statistically different from PBO at 16 wk	Composite adverse joint safety outcomes in 2.6% of TNZ, 10 mg; 1.0% of TNZ 5 mg; 0.2% of TRA

Abbreviations: FAS, fasinumab (subcutaneous); LBP, low back pain intensity; NSAID, non-steroidal anti-inflammatory drug (oral); OA, osteoarthritis; PBO, placebo; TNZ, tanezumab (subcutaneous); TRA, tramadol (oral).

respectively) and physical function (100-mm VAS; LS mean differences from placebo of -8.7 , -9.5 , -17.6 , respectively). Five study patients reported adverse events related to peripheral sensation, such as allodynia, paresthesia, thermohypoesthesia, and dysesthesia.³⁷ In summary, these phase II trials of tanezumab showed short-term efficacy in reducing pain and improving function in hip and knee OA, with adverse events of abnormal peripheral sensation.

Development of a different anti-NGF monoclonal antibody, fulranumab, occurred in parallel with the tanezumab trials. An early-phase study randomized 466 adults with moderate to severe OA pain of the hip or knee to receive subcutaneous fulranumab at various doses and frequencies, or placebo, both in addition to existing pain therapy. At week 12, those receiving the higher doses of fulranumab used in the study (3 mg every 4 weeks, 6 mg every 6 weeks, or 10 mg every 8 weeks) had improved WOMAC Pain subscale scores (0–10 NRS; LS mean differences from placebo -1.2 , -0.8 , and -0.9 , respectively) and WOMAC Physical Function subscale scores (0–10 NRS; LS mean differences from placebo -1.3 , -0.8 , and -1.3 , respectively). Neurologic adverse events were reported in 6% of the placebo group and 12% of patients treated with fulranumab, most commonly paresthesia and hypoesthesia.³¹ In a phase II double-blind extension of the previous study, participants were eligible to continue to receive those doses of fulranumab throughout a 92-week extension phase, followed by a 24-week post-treatment follow-up period. The duration of drug exposure was less than planned due to a Food and Drug Administration (FDA) hold on the anti-NGF development program for joint-related adverse safety signals (discussed in more detail later). Efficacy data were summarized, however, up to week 49. By this point, the fulranumab, 3 mg every 4 weeks and 10 mg every 8 weeks, group had improvements in WOMAC Pain and Physical Function subscales versus placebo throughout the study. The safety analysis revealed a joint safety signal of rapidly progressive OA (RPOA) in 15 of the 388 people (3.8%) receiving fulranumab and in none of the placebo group. All cases of RPOA occurred in patients taking both fulranumab and NSAIDs.³⁸ Another trial of fulranumab as monotherapy compared with placebo or oxycodone was terminated early due to an FDA hold on the anti-NGF development program for adverse safety signals, but in the limited number of patients randomized, fulranumab-treated patients had better pain relief than with controlled-release oxycodone, but not better than placebo.³⁹ Taken together, the early studies of fulranumab showed efficacy at pain reduction with the higher doses, with adverse events similar to the tanezumab trials.

PRE-FOOD AND DRUG ADMINISTRATION HOLD PHASE III TRIALS OF ANTI-NERVE GROWTH FACTOR AGENTS FOR HIP OR KNEE OSTEOARTHRITIS

In the first phase III study of IV tanezumab for knee OA, 690 patients were randomized to receive a single dose of IV tanezumab at 2.5 mg, 5 mg, or 10 mg or placebo. In this and subsequent studies of tanezumab, the investigators used fixed-dose regimens rather than those based on body weight. At week 16, those receiving tanezumab, 2.5 mg, 5 mg, and 10 mg, had reductions in WOMAC Pain, WOMAC Physical Function, and patient global assessment (PGA) compared with placebo. Similar to prior studies, those receiving tanezumab had adverse events of abnormal peripheral sensation.⁴⁰ In the first phase III trial of tanezumab for hip OA, 627 participants were randomized to IV tanezumab at 2.5 mg, 5 mg, or 10 mg doses or placebo. At 16 weeks, each group receiving tanezumab had reduced WOMAC Pain, WOMAC Physical Function, and Patient Global Assessment of OA (PGA-OA) scores versus placebo. As with previous trials, the tanezumab groups had more adverse events

compared with placebo, with abnormal peripheral sensation the most commonly reported.⁴¹ This phase III placebo-controlled trial of IV tanezumab, therefore, showed efficacy at reducing OA pain and improving physical function, with a similar safety signal to the early-phase studies.

Additional phase III studies compared IV tanezumab to other analgesics. One phase III study randomized participants to tanezumab, 5 mg or 10 mg every 8 weeks for 1 or 2 doses; or controlled-release oxycodone; or placebo. At week 8, both the 5-mg and 10-mg tanezumab groups had improvement in the WOMAC Pain compared with placebo and oxycodone (0–10 NRS; LS mean differences from placebo –0.96 and –0.96, respectively, and LS mean differences from oxycodone –0.99 and –0.99, respectively, for tanezumab, 5 mg and 10 mg), improvement in the WOMAC Physical Function score (0–10 NRS; LS mean differences from placebo –1.14 and –1.15, respectively, and LS mean differences from oxycodone –1.00 and –1.01, respectively, for tanezumab, 5 mg and 10 mg), with similar rate of adverse peripheral sensation as in other studies and an overall lower rate of adverse events in tanezumab arms compared with oxycodone.⁴² In 2 other randomized trials comparing IV tanezumab, 5 mg and 10 mg, against naproxen, 5-mg IV, tanezumab had superior improvement of WOMAC Pain score (0–10 NRS; LS mean differences –1.21 and –1.13 in 2 trials, respectively, vs placebo; LS mean differences –0.76 and –0.69 in 2 trials, respectively, vs naproxen), and improved WOMAC Physical Function and PGA over naproxen and placebo. The 10-mg IV tanezumab dose was only significantly better than naproxen for WOMAC Physical Function, not for WOMAC Pain or PGA. Overall rates of adverse events were similar for tanezumab and naproxen, although the 10-mg dose of tanezumab had more frequent peripheral abnormal sensation events.¹¹ These active-controlled phase III trials of IV tanezumab had short follow-up periods but demonstrated superior pain reduction and physical function with an overall favorable side-effect profile compared with opiate analgesics. When compared with oral NSAIDs, a typical first-line OA therapy, the results were mixed, with no superior pain relief at the higher tanezumab dose.

Additional studies examined the efficacy of IV tanezumab in combination with oral NSAIDs. In 1 study of individuals taking oral sustained-release diclofenac, 75 mg twice daily, for moderate to severe knee or hip OA, 607 participants were randomized to IV tanezumab, 2.5 mg, 5 mg, or 10 mg, or to placebo at weeks 0, 8, and 16. All continued diclofenac. At week 16, those receiving tanezumab and sustained-release diclofenac together had improvement over diclofenac plus placebo in WOMAC pain (0–10 NRS; LS mean differences from baseline –2.09, –2.19, and –2.25, respectively, and LS mean differences from placebo plus diclofenac –0.41, –0.51, and –0.57, respectively, in tanezumab, 2.5 mg, 5 mg, and 10 mg), with similar improvements in WOMAC Physical Function and PGA. The incidence of adverse events, however, was higher with combination therapy, including abnormal peripheral sensation, RPOA, and need for joint replacements.⁴³ Another study of patients with moderate to severe hip or knee OA expanded on these results by comparing tanezumab monotherapy with tanezumab combination therapy with NSAIDs versus NSAIDs treatment alone. In this study, 2700 individuals were randomized to receive IV tanezumab, 5 mg, 10 mg, or placebo, every 8 weeks, with or without oral naproxen or celecoxib. At 16 weeks, 5-mg and 10-mg tanezumab monotherapy improved WOMAC Pain and WOMAC Physical Function scores over NSAIDs alone, but no additional improvement was seen with combination therapy. Adverse events, however, were more frequent with tanezumab, especially with tanezumab and NSAIDs in combination, compared with NSAIDs therapy alone, primarily the development of RPOA.⁴⁴ Due to the high rate of adverse events seen in these combination trials of tanezumab and NSAIDs,

and other trials of fulranumab in patients taking NSAIDs, in particular RPOA, the combination of anti-NGF agents and NSAIDs is not recommended.

SAFETY CONCERNS AND FOOD AND DRUG ADMINISTRATION HOLD

In 2010, after reports arose of adverse events classified as osteonecrosis in the phase II and phase III trials of tanezumab for low back pain and hip or knee OA, respectively, the FDA placed a partial clinical hold on tanezumab and, subsequently, all other anti-NGF monoclonal antibodies, including fulranumab, for all indications except for cancer pain. An adjudication committee was formed by Pfizer, the results of which were presented to the FDA in 2012. Janssen Research & Development conducted a similar process for fulranumab. In the 11,712 participants in the phase 3 OA and phase 2 chronic low back pain (cLBP) tanezumab development programs, there were 87 reported cases of osteonecrosis, 55 of which occurred when tanezumab and NSAIDs were used in combination, 28 in tanezumab monotherapy, 4 in active comparator agents, and 0 with placebo. After adjudication, most of the osteonecrosis adverse events were reclassified as worsening OA (58.6%), of which two-thirds were RPOA. In addition, 24.1% of the osteonecrosis events were reclassified as other diseases, the most common of which was a subchondral insufficiency fracture of the knee. Data from the phase II studies in the fulranumab development program revealed increased rate of total joint replacements in participants receiving fulranumab (86 per 1000 patient-years) than with oxycodone (39.8 per 1000 patient-years) or placebo (50.8 per 1000 patient-years). These reviews confirmed the adverse safety signal of RPOA and total joint replacements with use of anti-NGF monoclonal antibodies. The rate of these complications was greater with the higher doses of the anti-NGF antibodies and concurrent use of NSAIDs in combination with tanezumab. The vast majority (85%) of those receiving fulranumab already were receiving NSAIDs.^{45,46}

After adjudication, most of the osteonecrosis events were reclassified as worsening or RPOA, and risk mitigation strategies were developed to reduce the risk of RPOA. These strategies included avoiding combination therapy with NSAIDs, using lower doses of anti-NGF agents administered subcutaneously, excluding patients with risk factors for RPOA or who would not be candidates for joint replacement, and establishing joint and neurologic safety monitoring protocols.⁴⁷ The FDA hold due to joint safety concerns was lifted in 2012.

Also in 2012, however, an additional clinical hold was placed due to reports of changes in the sympathetic nervous systems of animals receiving anti-NGF agents in nonclinical rodent studies. Three additional nonclinical studies of adult cynomolgus monkeys investigated the effect of subcutaneous tanezumab on the sympathetic nervous system. Tanezumab was associated with decreased sympathetic ganglia volume and average neuron size in the first month of treatment, but these changes were not associated with clinical deficits and reversed on drug withdrawal. There was no evidence found for adverse effects of sympathetic control of cardiovascular function (eg, orthostasis) nor evidence of neuronal cell death.⁴⁸ A study of fulranumab in adult cynomolgus monkeys similarly found decreased size of neurons and sympathetic ganglia, without evidence of neuronal cell death. The changes were found to be reversed after 3 months of drug withdrawal.⁴⁹ The clinical hold for sympathetic nervous system changes was lifted in 2015.

There is clinical evidence from case reports of skeletal disorders in some patients with congenital insensitivity to pain with anhidrosis, caused by loss-of-function mutations in either NGF or TrkA.^{50–53} In these patients, fracture healing was described as occurring normally, but some patients developed a progressive arthropathy, resulting

in disabling Charcot joints with gross deformity and instability. These patients lacked deep pain perception in bones and joints and had no protective reflexes, leading to significant bone and joint complications.⁵⁴

POST-2015 PHASE III STUDIES IN KNEE AND HIP OSTEOARTHRITIS

Development of tanezumab and fasinumab resumed after lifting of the FDA holds in 2015. A summary of these post-2015 trials is provided in [Table 1](#). In 1 phase III study, 698 participants with hip or knee OA who had not responded to or could not take standard OA analgesics were randomized to subcutaneous tanezumab, 2.5 mg, at week 1 and week 8; subcutaneous tanezumab, 2.5 mg, at week 1, and 5 mg at week 8; or placebo. At 16 weeks, WOMAC Pain scores (0–10 NRS) decreased from a mean of 7.1 to 3.6 in the tanezumab, 2.5-mg/2.5-m, group; from 7.3 to 3.6 in the tanezumab, 2.5-mg/5-m, group; and from 7.3 to 4.4 in the placebo arm (LS mean differences from placebo of –0.60 in the 2.5-mg/2.5-mg group and –0.73 in the 2.5-mg/5-mg group). There was a similar response in the WOMAC Physical Function score (0–10 NRS), with LS mean difference versus placebo of –0.66 for tanezumab, 2.5 mg/2.5 mg, and –0.89 for tanezumab, 2.5 mg/5 mg. Five patients in the tanezumab, 2.5-mg/2.5-m, arm (2.2%), and 1 patient in the tanezumab, 2.5-mg/5-m, arm (0.4%) developed RPOA versus no patients in the placebo group. Incidence rates of total joint replacement were 3.5%, 6.9%, and 1.7% in the tanezumab, 2.5-mg/2.5-mg; tanezumab, 2.5-mg/5-mg; and placebo groups, respectively.⁵⁵ In summary, lower doses of tanezumab administered subcutaneously reduced OA pain and improved function at 16 weeks but were associated with higher rates of RPOA and joint replacement compared to placebo.

Another phase III trial of subcutaneous tanezumab randomized 849 patients to receive tanezumab, 2.5 mg; tanezumab, 5 mg; or placebo every 8 weeks for 3 doses. At 24 weeks, the LS mean differences of tanezumab, 2.5 mg, compared with placebo was –0.46 for WOMAC Pain (0–10 NRS) and –0.59 for WOMAC Physical Function (0–10 NRS) but not significantly different than placebo for PGA-OA. For tanezumab, 5 mg, the LS mean differences from placebo were –0.62 for WOMAC Pain, –0.71 for WOMAC Physical Function, and –0.19 for PGA-OA (5-point Likert scale from 1 = very good to 5 = very poor). Safety findings were studied out to week 48. RPOA occurred in 0 patients receiving placebo; 4 patients (1.4%) receiving tanezumab, 2.5 mg; and 8 patients (2.8%) receiving tanezumab, 5 mg. There was 1 case of subchondral insufficiency fracture in the tanezumab, 2.5-mg group, and 1 case of primary osteonecrosis in the tanezumab, 5-mg, group. Rates of total joint replacement were 6.7% in placebo; 7.8% in tanezumab, 2.5 mg; and 7.0% in tanezumab, 5 mg. During the treatment period, paresthesia was more common with tanezumab, 5 mg (4.2%), than with placebo (1.8%) and equivalent to placebo in tanezumab, 2.5 mg (1.8%). Hypoesthesia was more common in tanezumab, 5 mg (2.1%), and in tanezumab, 2.5 mg (1.4%), than in placebo (0.7%). None of the paresthesia or hypoesthesia events was considered severe. There were no patients in any of the groups who developed sympathetic neuropathies, as confirmed by protocol-specified cardiology or neurology consultation.⁵⁶ This study had a longer duration of treatment and monitoring than in previous studies and showed efficacy for pain and physical function of both 2.5-mg and 5-mg doses of subcutaneous tanezumab but with a dose-dependent increasing in adverse joint events compared with placebo.

Additional information on the long-term efficacy and safety of subcutaneous tanezumab for hip or knee OA comes from a phase III active-controlled study of subcutaneous tanezumab compared with NSAIDs, currently published in abstract form (NCT02528188). In this trial, 2996 participants who had moderate to severe hip or

knee OA despite oral NSAIDs therapy either were switched to subcutaneous tanezumab or continued on oral NSAIDs. Patients received subcutaneous tanezumab (2.5 mg or 5 mg every 8 weeks) plus oral placebo, or oral NSAIDs plus subcutaneous placebo, continued from baseline through week 56, with an additional 24 weeks of safety monitoring. At week 16, those receiving tanezumab, 5 mg, had statistically significant improvement versus oral NSAIDs in WOMAC Pain (0–10 NRS; LS mean difference from NSAIDs -0.26) and in WOMAC Physical Function (0–10 NRS; LS mean difference from NSAIDs -0.31) but not in PGA-OA. The 2.5-mg tanezumab dose was not statistically different than NSAIDs therapy at week 16. Neither dose of tanezumab was statistically different than NSAIDs therapy at week 56.⁵⁷ The primary adjudicated composite joint safety outcome was defined as the combined rate of RPOA, osteonecrosis, subchondral insufficiency fracture, and pathologic fracture. At a total follow-up period of 80 weeks, the composite joint safety outcome occurred in 1.5% of the oral NSAIDs group; 3.8% of the tanezumab, 2.5-mg, group; and in 7.1% of the tanezumab, 5-mg, group. Most of these joint safety events were RPOA, occurring in 1.2% of the oral NSAIDs group; 3.2% of the tanezumab, 2.5-mg, group; and 6.3% in the tanezumab, 5-mg, group. Total joint replacement also was more common in tanezumab, 2.5 mg (5.3%), and in tanezumab, 5 mg (8.0%), than in those receiving oral NSAIDs (2.6%).⁵⁸ Although the lower dose of tanezumab, 2.5 mg, did not meet the efficacy endpoints versus oral NSAIDs in this study, the prolonged duration of treatment and follow-up provide the best information to date about the safety profile of tanezumab.

Fasinumab, a human anti-NGF monoclonal antibody, also is in phase III development. A phase IIb/III study randomized 421 individuals with hip or knee OA and inadequate response to analgesics to subcutaneous fasinumab at doses ranging from 1 mg to 9 mg every 4 weeks or placebo. At week 16, all doses of fasinumab led to decreased WOMAC Pain score (0–10 NRS; LS mean difference from placebo ranging from -0.8 to -1.4), with similar improvements in WOMAC Physical Function and PGA, with no obvious dose dependence observed. Adjudicated analysis found arthropathy adverse events in 5% of the study overall, involving 25 joints (13 index and 12 nonindex) in 7% of those in the fasinumab groups and 1% in the placebo group. The arthropathies demonstrated a dose relationship. RPOA occurred in 5% of the fasinumab and 0% of the placebo group, and subchondral insufficiency fractures in 1.8% of the fasinumab and 1.2% in the placebo group. The rates of joint replacement, approximately 4%, were similar in all groups. Most arthropathies were detected radiographically.⁵⁹

As of the date of this publication, fulranumab is not in active development. Fasinumab is in ongoing phase III trials. The developer of tanezumab has submitted a biologics license application to the US Food and Drug Administration for the 2.5-mg dose of subcutaneous tanezumab for the treatment of moderate to severe OA.

ANTI-NERVE GROWTH FACTOR AGENTS FOR CHRONIC LOW BACK PAIN

Early studies of anti-NGF agents tanezumab, fulranumab, and fasinumab for cLBP showed mixed results in reducing pain versus placebo and shared the same joint safety concerns as in trials for hip and knee OA.⁶⁰ After lifting of the FDA hold in 2015, development of anti-NGF agents for cLBP resumed. Important outcome measures in these trials include the low back pain intensity (LBPI) score (0–10 NRS with 0 = no pain and 10 = most severe pain) and the Roland-Morris Disability Questionnaire (RDQ) (24-item assessment of daily physical function scored from 0 = no disability to 24 = maximum disability).⁶¹

The first phase III study of subcutaneous tanezumab randomized 1832 patients with cLBP and inadequate response to analgesics to receive subcutaneous tanezumab, 5 mg or 10 mg, every 8 weeks, or placebo, or prolonged-release oral tramadol. At 16 weeks, tanezumab, 10 mg, provided significantly better improvement in LBPI than placebo (LS mean difference vs placebo -0.40) and better improvement in RDQ than placebo (LS mean difference vs placebo -1.74). Improvements with tanezumab, 5 mg, were not significantly different than placebo at week 16. Neither tanezumab dose was superior to tramadol at reducing LBPI at 16 weeks, although tanezumab, 10 mg, provided greater reduction in RDQ than tramadol. There was no significant difference in LBPI or RDQ with tanezumab compared with placebo or tramadol at week 56. Joint safety adjudication revealed more frequent adverse joint safety outcomes in the tanezumab, 10-mg, group (2.6%) than in the tanezumab, 5-mg, group (1.0%), or than in the tramadol group (0.2%). The most frequent adverse joint outcome was RPOA (1.4% in the tanezumab, 10-mg, group) in 80 weeks' total follow-up.⁶²

SUMMARY

NGF inhibitors reduce pain and improve physical function in patients with moderate to severe hip or knee OA. The anti-NGF antibodies currently under development are administered by subcutaneous injection every 4 weeks to 8 weeks, providing a prolonged duration of pain relief. Enthusiasm for these agents has been limited primarily by the development of RPOA and other adverse joint events that are dose-dependent safety signals seen with administration of anti-NGF agents, particularly because the mechanism behind these events is not entirely clear. The magnitude of and mechanism behind the further increased risk of RPOA when anti-NGF agents are combined with NSAIDs also are not defined. Relatively mild neurologic adverse events also have been reported. Trials have been relatively short term, and, given the chronic continuous nature of OA, the rates of RPOA and joint replacement during long-term use of anti-NGF agents also are not yet clear and remain areas of active investigation. In the largest recent studies, RPOA occurred in 2.4% to 8.4% of those receiving subcutaneous fasinumab at various doses for 16 weeks of treatment at 36 weeks' total follow-up⁵⁹; in 3.2% of those receiving subcutaneous tanezumab, 2.5 mg; and 6.3% of those receiving tanezumab, 5 mg, for 56 weeks of treatment at 80 weeks' total follow-up.⁵⁸ Thus, the benefit of anti-NGF therapy to reduce pain and improve function must be balanced cautiously against the risk of accelerated OA. Further studies are needed to determine the mechanisms underlying the development of RPOA, which may enable identifying patients at higher or lower risk, which would enable a more personalized medicine approach to use of anti-NGF therapy.

CLINICS CARE POINTS

- Anti-NGF monoclonal antibodies are being considered for FDA approval for use in OA of the hip or knee.
- RPOA is a safety signal observed in NGF inhibitor trials that remains poorly understood.
- NGF inhibitors never should be used concurrently with NSAIDs due to an enhanced risk of RPOA when both agents are used together.
- The benefit of anti-NGF therapy to reduce pain and improve function must be balanced cautiously against the risk of accelerated OA.

DISCLOSURE

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