

Anti-nerve growth factor in pain management: current evidence

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Abstract: There continues to be an unmet need for safe and effective pain medications. Opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) dominate the clinical landscape despite limited effectiveness and considerable side-effect profiles. Although significant advancements have identified myriad potential pain targets over the past several decades, the majority of new pain pharmacotherapies have failed to come to market. The discovery of nerve growth factor (NGF) and its interaction with tropomyosin receptor kinase A (trkA) have been well characterized as important mediators of pain initiation and maintenance, and pharmacotherapies targeting this pathway have the potential to be considered promising methods in the treatment of a variety of nociceptive and neuropathic pain conditions. Several methodologic approaches, including sequestration of free NGF, prevention of NGF binding and trkA activation, and inhibition of trkA function, have been investigated in the development of new pharmacotherapies. Among these, NGF-sequestering antibodies have exhibited the most promise in clinical trials. However, in 2010, reports of rapid joint destruction leading to joint replacement prompted the US Food and Drug Administration (FDA) to place a hold on all clinical trials involving anti-NGF antibodies. Although the FDA has since lifted this hold and a number of new trials are under way, the long-term efficacy and safety profile of anti-NGF antibodies are yet to be established.

Keywords: nociceptive pain, neuropathic pain, drug discovery, tanezumab, fulranumab, fasinumab

Introduction

Chronic pain is a disease unto itself, a state in which the protective role of pain transmission becomes deranged and pathologic. According to a 2010 analysis,¹ chronic pain affects ~100 million Americans at an estimated annual cost of US\$560–US\$635 billion. The public health and economic burden of chronic pain is enormous and indicative of both the complexity of the disease as well as the limitations of current treatment modalities.

Despite their limited effectiveness for many chronic pain conditions and considerable side-effect profile, opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) continue to dominate clinical practice.² It is largely believed that mechanism-based treatments, rather than disease- or diagnosis-based treatments, hold the key to the development of new successful therapies.³ Shortcomings in the pharmacologic management of pain are thought to be attributed to a failure to target underlying mechanisms of chronic pain.³ Although tremendous strides have been made over the past several decades to better understand pain pathophysiology and identify potential drug therapies, the vast majority of new pharmacotherapies have failed in clinical

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trials.⁴⁻⁶ In fact, a 2015 scientometric analysis⁶ suggests that interest in analgesic drug discovery by the pharmaceutical industry is waning. It is within this context that nerve growth factor (NGF) and its related molecular targets represent a completely novel therapy mode, with potentially broad clinical applications for both nociceptive and neuropathic pain conditions.

NGF background

NGF was initially discovered in the 1950s as a tumor tissue-produced soluble factor that promotes the growth and differentiation of sensory and sympathetic ganglia.^{7,8} NGF was the first growth factor to be identified and its discovery represented a landmark achievement in developmental neurobiology. The illumination of NGF's critical role in neuronal development eventually led to the creation of the "neurotrophic factor hypothesis" and the classical neurotrophic model in which NGF is synthesized and released by target tissues during embryonic development, promoting the growth, differentiation, and survival of neurons in a dose-dependent manner.^{7,9} Subsequent studies have broadened our understanding of this process and the role that neurotrophic factors play in the mammalian nervous system.^{7,8}

NGF belongs to a family of neurotrophic factors or neurotrophins comprising brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4). Neurotrophins act by binding to two types of cell surface receptors: neurotrophin receptor (NGFR or p75) and a family of tyrosine kinase receptors, tropomyosin-related kinase A (trkA), trkB, and trkC. All neurotrophins bind NGFR/p75 with similar affinity, but each neurotrophin binds preferentially to a specific trk receptor; NGF preferentially binds trkA, BDNF binds trkB, and NT-3 binds trkC.¹⁰ TrkA is highly expressed by sensory neurons of the dorsal root ganglia (DRG) during embryogenesis; however, by the post-natal period, trkA expression and NGF sensitivity decline, and the role of NGF-trkA signaling shifts from promoting neuron growth and survival to regulating the sensitivity of the peripheral nervous system to noxious stimuli.¹¹

Rationale: NGF and pain

NGF levels are elevated in preclinical models of both inflammation and peripheral nerve injury. Clinically, NGF concentration is increased in chronic pain conditions such as interstitial cystitis, prostatitis, arthritis, pancreatitis, chronic headaches, cancer pain, diabetic neuropathy, and noncancer pain, suggesting that NGF-mediated signaling is an ongoing and active process in chronic nociceptive and neuropathic

pain states.^{10,12-14} A number of studies¹⁴⁻¹⁶ involving direct intradermal injection of NGF in rodents and humans have demonstrated a clear functional role for NGF in both activation and sensitization of nociceptors.¹⁴⁻¹⁶

Mechanism of action in nociceptive pain

Nociceptive pain occurs through the activation of nociceptors located in peripheral tissues in response to noxious stimuli. A noxious stimulus is any stimulus (eg, chemical, thermal, or mechanical) that either damages or threatens to cause damage to normal tissues.⁴ NGF is produced and released by peripheral tissues following noxious stimuli (eg, injury and inflammation) secondary to the production of inflammatory cytokines, such as interleukin-1 and tumor necrosis factor-alpha. NGF binds to trkA receptors on multiple targets, with multiple modulating effects on pain signaling.¹⁴

NGF binds to trkA that is selectively expressed on the peripheral terminals of A-delta and peptidergic unmyelinated C-fibers.^{10,14} The NGF-trkA complex is then internalized and transported retrogradely to DRG cell bodies, modulating and/or increasing the expression of a variety of cell surface receptors involved in nociception, including bradykinin receptors, acid-sensing ion channels (ASIC) 2/3, voltage-gated sodium channels, voltage-gated calcium channels, delayed rectifier potassium channels, putative mechanotransducers, as well as transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor-mediated currents (Figure 1). There is some debate over whether the increase in TRPV1 signaling is due to a decrease in the TRPV1 activation threshold or an increase in receptor trafficking to the cell surface.^{13,17-19} Nevertheless, the increase in TRPV1 signaling and the increased activity of other channels result in peripheral sensitization and pain hypersensitivity. NGF-trkA signaling also leads to transcriptional changes that result in the increased expression of the pronociceptive neurotransmitters substance P (SP), calcitonin gene-related peptide (CGRP), and BDNF, thereby leading to central sensitization (Figure 1).^{13,14}

An additional effect of NGF on pain processing occurs through its binding of trkA receptors located on mast cells. This process is proinflammatory and elicits the release of inflammatory mediators such as histamine, serotonin or 5-hydroxytryptamine (5-HT), protons, as well as NGF itself, resulting in a positive feedback loop (Figure 1).^{13,14} Thus, not only does NGF signaling increase the expression of peripheral nociceptive receptors and centrally located pronociceptive neurotransmitters, but it also sensitizes adjacent nociceptive neurons in response to inflammation.

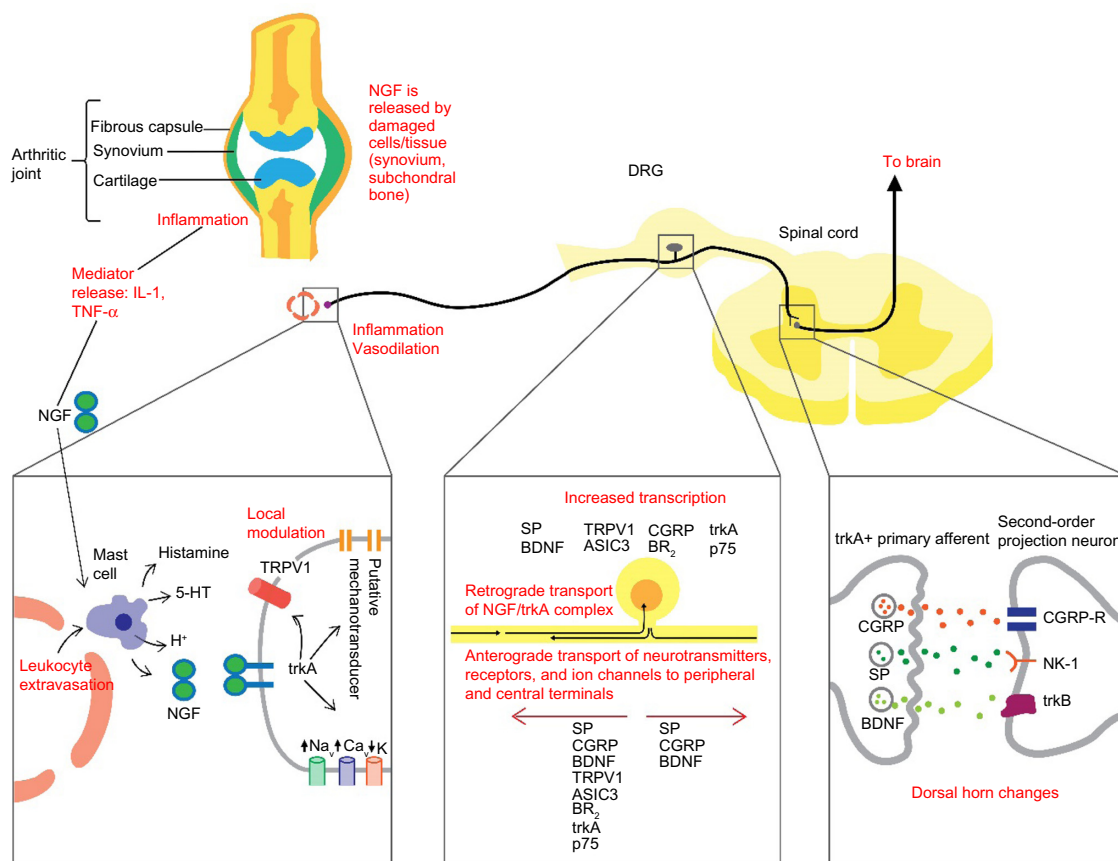


Figure 1 Schematic diagram of the NGF mechanisms involved in the initiation and maintenance of pain.

Note: Drawing courtesy of Caitlin Hottinger.

Abbreviations: 5-HT, 5-hydroxytryptamine; ASIC3, acid-sensing ion channel 3; BDNF, brain-derived neurotrophic factor; BR₂, bradykinin receptor 2; Ca_v, voltage-gated calcium channel; CGRP, calcitonin gene-related peptide; CGRP-R, calcitonin gene-related peptide receptor; DRG, dorsal root ganglia; IL-1, interleukin 1; K, delayed-rectifier potassium channel; Na_v, voltage-gated sodium channel; NGF, nerve growth factor; NK-1, neurokinin 1 receptor; p75, neurotrophin receptor; SP, substance P; TNF-α, tumor necrosis factor alpha; trkA, tropomyosin receptor kinase A; trkB, tropomyosin receptor kinase B; TRPV1, transient receptor potential cation channel subfamily V member 1 receptor.

Mechanism of action in neuropathic pain

Neuropathic pain results from damage to the neurons of the somatosensory system, secondary to either direct injury or disease-related dysfunction, and results in the generation of ectopic discharges that occur independently of somatic stimuli.⁴ As mentioned previously, NGF levels are generally increased in chronic neuropathic conditions such as diabetic neuropathy and cancer pain, in particular, invasive nerve cancers.^{20,21} But the relationship between NGF signaling and neuropathic pain states is complex, and in some patients with diabetic neuropathy, NGF levels are actually decreased.²¹ In patients with chemotherapy-induced peripheral neuropathy, a decrease in circulating NGF is correlated with an increased severity of neuropathy.⁸ In preclinical studies, NGF has demonstrated a trophic and neuroprotective action on peptidergic small-diameter DRG cells after nerve injury,²² and a number of clinical studies have been conducted investigating the negative correlation between NGF levels and peripheral

neuropathy by examining the administration of subcutaneous injections of recombinant NGF.⁸ In a Phase II trial²³ involving patients with diabetic neuropathy, endogenous NGF administration resulted in relief of neuropathic pain, whereas a subsequent Phase III trial²⁴ found no difference in neuropathic symptoms compared to placebo. In patients with HIV-associated peripheral neuropathy, two completed Phase II studies exhibited mixed results.^{25,26} It is noteworthy to mention that all clinical studies^{23–26} have reported significant dose-dependent hyperalgesia at the site of NGF injection. NGF administration has also shown the ability to induce nerve sprouting of trk-A-positive nociceptive as well as sympathetic nerve fibers, while NGF blockade by systemic injection of neutralizing antibodies in models of neuropathic pain appears to prevent allodynia and hyperalgesia.^{14,21} Mechanistically, NGF sequestration has demonstrated inhibition of neuroma formation and a decrease in ectopic discharges. In models of bone cancer, where neuroma formation and reorganization

of sensory and sympathetic fibers is prominent, the administration of an NGF-sequestering antibody prevents this pathologic reorganization and inhibits the development of cancer pain.²⁷

Pharmacotherapy

A number of approaches have been developed to target the NGF pathway and its effect on pain initiation and maintenance. The majority of these efforts have centered on the NGF–trkA pathway and focus on three methodologic approaches: 1) sequestration of free NGF; 2) prevention of NGF binding and activation of trkA; and 3) inhibition of trkA function.^{10,14}

NGF-sequestering agents

Preclinical studies

Antibodies possess significant advantages compared to small molecules due to generally higher specificity and reduced off-target effects, culminating in quicker clinical development and faster US Food and Drug Administration (FDA) approval.¹² Preclinical studies^{14,28} involving pretreatment with systemic anti-NGF antibody have shown successfully reduced acute thermal and mechanical hypersensitivity in response to Freund's adjuvant in models of inflammatory pain. This preventative effect is also observed in models of visceral inflammation such as acetic acid-induced gastric inflammation and acrolein-induced cystitis.^{29,30} In models of established pain, such as visceral hyperalgesia involving trinitrobenzene sulfonic acid-induced colonic hypersensitivity, anti-NGF antibody administration has demonstrated the ability to reverse colonic hypersensitivity.³¹ An additional study³² involving the use of NGF antibodies in models of autoimmune arthritis have demonstrated analgesia equivalent to indomethacin despite continued joint destruction and inflammation. Anti-NGF administration has also resulted in significant analgesic effects in the treatment of hypersensitivity associated with chronic injury models of bone cancer and closed femur fracture, effectively reducing the neurochemical changes associated with peripheral and central sensitization.^{33,34} To highlight the specificity of anti-NGF antibody therapy in each of these models, despite significant reductions in pain after fracture and tumor growth, the density and number of sensory and sympathetic fibers were not affected.^{33,34} Furthermore, in models of inflammatory pain, NGF blockade shows reduced inflammation-mediated hypersensitivity but does so without altering other inflammatory processes such as erythema and edema.^{14,28} Additional preclinical work has also revealed no effect of anti-NGF therapy on bone healing after fracture.³⁵

Clinical trials

Osteoarthritis

Phase I studies investigating tanezumab were initially reported in 2005, and a subsequent proof-of-concept Phase II trial in patients with moderate-to-severe knee osteoarthritis (OA) who had an unsatisfactory response to nonopioid pharmacotherapy, demonstrated dose-dependent efficacy and treatment-related adverse effects compared to placebo, with hypoesthesia and paresthesias being the most prominent.^{36–38} Dosing ranges in these Phase II studies included 10 µg/kg, 25 µg/kg, 50 µg/kg, 100 µg/kg, and 200 µg/kg administered intravenously (IV) at an 8-week interval, with follow-up conducted at a minimum of 8 weeks after the last dose.^{36,39,40} Subsequently, five placebo-controlled Phase III studies^{36,41–44} involving tanezumab in patients with hip and/or knee OA found statistically significant benefit across dosing ranges of 2.5 mg, 5 mg, and 10 mg, as assessed by the Western Ontario and McMaster Universities Osteoarthritis Index subscales. Fulranumab and fasinumab have also been studied in patients with chronic hip/knee OA and knee OA, respectively, and both medications demonstrated significant analgesia compared to placebo, with a low incidence of adverse effects.^{45,46} When assessed in a 2015 systematic review and meta-analysis that included 13 randomized controlled trials (ten tanezumab, two fulranumab, and one fasinumab), all anti-NGF agents across a variety of dosages were superior to placebo, and the three studies comparing tanezumab monotherapy to an active control (NSAID or opioid) also demonstrated superior efficacy (Table 1).^{36,39–50}

Low back pain

In a 2011 proof-of-concept study,⁵¹ 220 patients with chronic nonradicular low back pain (LBP) were administered a single dose of IV tanezumab 200 µg/kg plus oral placebo, IV placebo plus naproxen twice daily, or IV placebo plus oral placebo. At 6 weeks, compared to both naproxen and placebo, patients in the tanezumab treatment arm exhibited significantly greater reductions in pain intensity and corresponding improvements in physical function.⁵¹ A subsequent Phase II study⁵² also performed in patients with chronic mechanical LBP extended IV tanezumab therapy to two doses administered at an 8-week interval. Study arms included three fixed doses of 5 mg, 10 mg, and 20 mg, as well as IV and oral placebos and naproxen, in a double-blind, double-dummy design, in which all patients received two doses of IV treatment and daily oral administrations. The investigators found that both 10 mg and 20 mg dosages exhibited efficacy in pain and physical function at 16 weeks, which was statistically

Table 1 Summary of evidence: monoclonal anti-NGF antibodies

Compound	Summary of evidence	CLBP	DN and PHN	Visceral pain	Cancer pain
Tanezumab	Strong evidence of efficacy, shown to be superior to active controls (NSAID and opioids); long-term safety study in active recruitment phase	In patients with nonradiculopathic CLBP, higher dose range (10 mg and 20 mg) demonstrated efficacy and superiority to naproxen	Single study in DN demonstrated efficacy at 20 mg dose; single study in PHN failed to demonstrate efficacy	In patients with interstitial cystitis, single dose improved pain and reduced urgency; in patients with chronic prostatitis/chronic pelvic pain syndrome, neither pain nor urgency reached significance	Single 10 mg dose did not achieve significance, but treatment continued up to 40 weeks demonstrated pain below baseline levels; post hoc analysis suggested that lower baseline opioid use and/or greater baseline pain was predictive of benefit
Fulranumab	Strong evidence of efficacy; in need of long-term safety study due to concern for rapidly progressive OA	In patients with nonradiculopathic CLBP, it was not superior to placebo in single Phase II trial	Single study in DN demonstrated dose-response relationship and efficacy only at highest dose (10 mg)		
Fasinumab	Strong evidence of efficacy; in need of long-term safety study due to concern for rapidly progressive OA	A single study in which patients with sciatic pain demonstrated no benefit			

Abbreviations: CLBP, chronic low back pain; DN, diabetic neuropathy; NGF, nerve growth factor; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; PHN, postherpetic neuralgia.

superior to both placebo and naproxen; the 5 mg dose was significant vs placebo at 4 weeks, 8 weeks, and 12 weeks, but not at 16 weeks, and was not superior to naproxen at any time point.⁵² A successive open-label extension study,⁵³ whose objective was to further evaluate the long-term safety and efficacy of tanezumab, took patients from the aforementioned 16-week parent study⁵² and rerandomized them to receive either three IV injections of 10 mg or 20 mg of tanezumab, followed by four subcutaneous injections at the same dose every 8 weeks. Patients who had received 10 mg or 20 mg in the parent study⁵² were maintained on the same dose for the extension study.⁵³ At 4 weeks, 8 weeks, 16 weeks, and 24 weeks of the extension study,⁵³ all patients reported improvements in pain from baseline, with slightly greater efficacy in the 20 mg group vs the 10 mg treatment group. Additional Phase II studies^{54,55} in patients with chronic LBP have been undertaken with the NGF-neutralizing antibodies fulranumab and fasinumab. Subcutaneous injections of fulranumab in doses ranging from 1 mg to 10 mg at 4-week intervals failed to achieve a significant reduction in average pain at Week 12.⁵⁴ Fasinumab administered to patients with radicular pain as a single subcutaneous injection at doses of 0.1 mg/kg (n=54) and 0.3 mg/kg (n=54) demonstrated no benefit for average daily back or leg pain at 4 weeks compared to placebo (n=51).⁵⁵

Diabetic neuropathy and postherpetic neuralgia

A number of anti-NGF proof-of-concept clinical studies have been conducted in patients with diabetic neuropathy.^{56,57} Tanezumab administered as a single IV dose of 20 mg resulted in significant reductions in average pain scores at 4 weeks and 8 weeks after treatment, with 39.6%, 31.6%, 21.1%, and 13.2% experiencing $\geq 30\%$, $\geq 50\%$, $\geq 70\%$, and $\geq 90\%$ pain reduction, respectively.⁵⁶ In a Phase II double-blind placebo-controlled trial,⁵⁷ fulranumab given as a subcutaneous injection of 1 mg, 3 mg, or 10 mg at 4-week intervals demonstrated dose-dependent efficacy, with the 10 mg dose resulting in superior relief compared to placebo at 12 weeks. At the 10 mg dose, 60.9% and 30.4% of patients reported $\geq 30\%$ and $\geq 50\%$ relief, respectively. A post hoc analysis⁵⁷ revealed that Neuropathic Pain Symptom Inventory scores in burning (superficial) spontaneous pain $>5/10$ or pressing (deep) spontaneous pain $>3.5/10$ were more likely to respond to treatment, suggesting that phenotypic differences within this population may predict response to anti-NGF therapy, and that perhaps the variable increase or decrease in NGF levels in patients may also play a predictive role. In contrast, a parallel group study by Bramson et al⁵⁶ examining

tanezumab in patients with postherpetic neuralgia failed to yield significant reductions in average pain score.

Visceral pain

Tanezumab has been studied in two small-scale proof-of-concept trials^{58,59} involving chronic visceral pain. Patients with interstitial cystitis were administered a single dose of IV tanezumab 200 µg/kg (n=34) or placebo (n=30), with a primary end point of change in average daily pain score from baseline to 6 weeks. Patients in the tanezumab arm not only experienced a statistically significant reduction in pain scores vs placebo but also displayed reduced urgency episode frequency.⁵⁸ In a study⁵⁹ evaluating patients with moderate-to-severe chronic prostatitis/chronic pelvic pain syndrome, 30 patients received a single IV dose of tanezumab (20 mg) and 32 received a placebo. Although average pain score and urgency episode frequency trended downward at 6-week follow-up, neither outcome achieved significance.⁵⁹

Cancer pain

A single study in patients with metastatic bone cancer involved an initial 16-week placebo-controlled parent study, followed by a 40-week uncontrolled open-label extension period.⁶⁰ In the parent study, 59 patients were randomized and treated with an initial 10 mg IV tanezumab infusion (n=29) or placebo (n=30). Whereas no significant change was observed in daily average pain scores, a post hoc analysis suggested greater efficacy, with lower baseline opioid use and/or greater baseline pain. It should be noted that by Week 8, 48.3% of tanezumab-treated patients reported a $\geq 30\%$ reduction in pain compared to only 20% in the placebo group, though no significant difference was observed in patients reporting $\geq 50\%$, $\geq 70\%$, and $\geq 90\%$ improvement in average pain scores. In the 40-week extension, patients received 10 mg IV tanezumab infusions at 8-week intervals. These individuals experienced a significant decrease in pain scores compared to the baselines in the parent and extension studies⁶⁰ at Week 8, with 43.3% and 36.7% of patients reporting $\geq 30\%$ and $\geq 50\%$ reductions in average daily pain, respectively, and, through Week 40, had improvements of -1.27 (0.68) and -1.40 (0.60) for average daily pain and daily worst pain, respectively.

Safety

In one recent review, Bannwarth and Kostine⁶¹ found that the most common treatment-related side effects of anti-NGF therapy were peripheral edema, arthralgia, extremity pain, and neurosensory symptoms (paresthesia and hypoesthesia).

Moreover, treatment-related adverse events were similar for all anti-NGF therapies, suggestive of a class-specific effect. In the largest randomized controlled trial⁵⁰ to date, 2,700 subjects with knee or hip OA receiving inadequate relief on a stable oral NSAID regimen were randomized into five treatment groups receiving IV tanezumab 5 mg (plus NSAID or oral placebo), tanezumab 10 mg (plus NSAID or oral placebo), or IV placebo plus NSAID; the study did not include an IV placebo plus oral placebo group. At 16 weeks, after all study patients received at least one IV treatment, the frequencies of the majority of adverse events were similar between the 5 mg and 10 mg tanezumab doses, with the exception of paresthesias and pain in the extremity, which were slightly more frequent at 10 mg in both the NSAID-combined and placebo-combined treatment arms (paresthesias: 11.1% vs 9.0% and pain in extremity: 5.5% vs 3.9% in the NSAID-combined group; paresthesias: 9.0% vs 7.2% and pain in extremity: 6.6% vs 3.5% in the placebo-combined group). A number of adverse events were more common in the tanezumab-plus-NSAID group compared to the group on mono-NGF therapy, such as peripheral edema (at 5 mg, 7.1% vs 6.1%; at 10 mg, 9.2% vs 5.0%), paresthesias (at 5 mg, 9.0% vs 6.1%; at 10 mg, 11.1% vs 7.2%), and hypoesthesias (at 5 mg, 6.5% vs 4.6%; at 10 mg, 6.5% vs 5.7%), whereas joint swelling (at 5 mg, 3.4% vs 4.1%; at 10 mg, 3.1% vs 5.0%) was less common in the combination treatment group compared to that in monotherapy group.⁵⁰ In a meta-analysis of anti-NGF treatment in OA patients, overall odds ratio (OR) for withdrawals due to adverse events in all patients receiving tanezumab monotherapy was 1.50 (95% confidence interval [CI]: 0.94–2.38) compared to placebo.³⁶ However, no statistical difference was observed in rates of withdrawal with the 2.5 mg (OR: 1.23; CI: 0.5–3.02) and 5.0 mg (OR: 1.09; CI: 0.55–2.16) doses relative to the placebo. The 10 mg dose had an OR of 1.92 (CI: 1.20–3.09), suggesting that some adverse effects are dose dependent.³⁶ In a similar population and study design, the rates of withdrawal due to adverse effects with fulranumab (OR: 1.77; CI: 0.74–4.22) or fasinumab (OR: 1.53; CI: 0.50–4.73) failed to reach statistical significance.³⁶ In the meta-analysis³⁶ of the tanezumab-plus-NSAID combination therapy vs NSAID alone in OA patients, withdrawals due to adverse events reached statistical significance (OR: 1.90; CI: 1.39–2.61). Moreover, the incidence of serious adverse events was also higher in the combination group compared to the NSAID-alone group (OR: 1.39; CI: 1.00–1.94). Nevertheless, the overall incidence of adverse events was small, and anti-NGF therapy was generally well-tolerated. However, in 2010, all clinical trials for anti-NGF antibodies were put on

hold by the FDA due to reports of rapidly progressive OA and osteonecrosis leading to joint replacement. Reported cases occurred in OA subjects receiving tanezumab, tanezumab-plus-NSAID, or fulranumab and involved extensive bone damage and joint destruction. Several cases occurred in multiple joints and nonindex joints, including shoulders. Pfizer (New York, NY, USA) and Janssen (Beerse, Belgium), the manufacturers of tanezumab and fulranumab, respectively, each assembled separate multidisciplinary adjudication committees comprising bone pathologists, orthopedic surgeons, and rheumatologists, charged with reviewing all reports of osteonecrosis leading to joint replacement.⁶² The tanezumab adjudication included a total of 87 subjects, 81 of whom were enrolled in Phase III OA studies and six who were enrolled in Phase II chronic LBP studies.⁶² Review of all available case reports diagnosed osteonecrosis and rapid OA progression in two (2.3%) and 34 (66.7%) subjects, respectively. The remaining cases were distinguished as normal OA progression (n=17, 33%), other diseases (n=21, 24.1%), lacking a consensus (n=5, 5.8%), and lacking sufficient information for a determination (n=8, 9.2%). In the fulranumab adjudication, among 1,353 subjects, 88 reported at least one joint replacement and, in total, there were 101 joint replacements (97 initial replacements and four revisions).⁶³ Moreover, 65 (65%) of these cases were determined to be due to normal OA progression, 18 (18%) were classified as rapidly progressive OA, 14 (14%) cases lacked sufficient information for a determination, and the four (4%) revisions were considered not applicable. In 2012, the FDA commissioned an independent arthritis advisory committee to further investigate these claims and concluded that joint failures were probably related to anti-NGF treatment and represented a unique clinical form of rapidly progressive OA, citing rapid and considerable joint destruction, typically within 6–12 months of exposure. These cases were characterized by particular pathological features, including femoral head flattening and medial femoral condyle involvement with subchondral fractures, as well as associated edema, joint effusions, and marked pain.⁶⁴ The committee also determined that events were more likely to occur with longer exposures and concurrent NSAID use, possibly through the inhibition of bone healing. Although the precise etiology was not clear, several plausible mechanisms were discussed, including higher susceptibility in patients with atrophic and neuropathic forms of OA, subchondral bone pathology, overuse of joints, and possible drug toxicity with concurrent NSAID use. Nevertheless, the committee conceded that more study was needed to fully understand the risk of anti-NGF therapy to bones and joints, in addition

to voting in favor of continued development of the drug class due to the potential benefit of anti-NGF therapy for a multitude of pain conditions and the absence of any direct link between the administration of anti-NGF antibodies and joint destruction.^{61,65} Whereas a number of measures to mitigate the risks were discussed, such as limiting trials to the use of the lowest effective doses, restriction of NSAID use, and the development of a screening radiologic protocol, no consensus criteria for study continuation has been reached to date.^{61,66} In 2013, after negotiations between pharmaceutical companies and the FDA, the FDA issued a notification to Pfizer that the “clinical hold” for tanezumab would be lifted pending submission and review of nonclinical data.⁶¹ A recent search of the National Institutes of Health Web site “clinicaltrials.gov” revealed two ongoing long-term safety and efficacy studies^{67,68} evaluating tanezumab monotherapy in patients with OA of the hip or knee, as well as in patients with chronic LBP. There are four fulranumab studies^{69–72} in active recruitment for patients with OA, two of which will evaluate its adjunctive use with other medications, including NSAIDs. There is also ongoing recruitment for a Phase I trial evaluating fasinumab.⁷³

NGF–trkA binding inhibitors

Initially developed for the characterization of the NGF–trkA signaling pathway, mouse monoclonal anti-trkA, MNAC13, is capable of inducing analgesia in models of inflammatory (formalin injection) and neuropathic pain (sciatic nerve ligation).²⁰ When used in combination with low-dose opioids, the class demonstrates a synergistic effect. However, the inability to develop an equivalent humanized antibody has prevented the introduction of an analogous species into clinical trials. The nonpeptide small molecule ALE0540 is an NGF inhibitor that prevents NGF binding to both trkA and p75.⁷⁴ Despite its demonstrated antinociceptive effect in animal models of neuropathic pain following intrathecal administration, ALE0540 appears to suffer from a lack of specificity when tested with other receptors *in vitro* and thus has not been advanced into clinical trials (Table 2).

Inhibitors of trkA

k252a is a small-molecule protein kinase inhibitor that inhibits the activation of the entire tropomyosin receptor kinase family (trkA, trkB, and trkC). In a rat model of acute necrotizing pancreatitis, k252a administration reversed DRG CGRP and SP upregulation and alleviated mechanical hypersensitivity.⁷⁵ However, due to lack of specificity, no human

Table 2 Summary of evidence: NGF–trkA binding inhibitors and trkA inhibitors

Compound	Mechanism of action	Summary of evidence
MNAC13	Monoclonal anti-trkA antibody	Analgesia in mouse models of inflammatory and neuropathic pain; possible synergistic effect with opioids; mouse antibody with no equivalent humanized antibody
ALE0540	NGF inhibitor, prevents NGF binding to both trkA and p75	Reduces pain behavior in animal models of neuropathic pain; deemed unsuitable for clinical trial due to lack of specificity
K252a	Protein kinase inhibitor, inhibits trkA, trkB, and trkC	Reverses mechanical hypersensitivity in model of acute necrotizing pancreatitis; deemed unsuitable for clinical trial due to lack of specificity

Abbreviations: NGF, nerve growth factor; p75, neurotrophin receptor; trkA, tropomyosin receptor kinase A; trkB, tropomyosin receptor kinase B; trkC, tropomyosin receptor kinase C.

trials have ever been initiated and no additional compounds targeting trkA activation have been developed to date, underscoring the challenges in targeting a single component of a pervasive receptor class.

Other potential targets

As efforts continue to be made to further characterize the NGF–trkA pathway, additional molecular targets are likely to emerge. One such target is the trkA-specific Q-SNARE protein, Syntaxin 8 (STX8).⁷⁶ STX8 facilitates trkA receptor transport from the Golgi apparatus to the plasma membrane. Furthermore, knockdown of *STX8* in rat DRG resulted in analgesia in models of inflammatory pain and could eventually lead to the generation of additional pain therapeutics.⁷⁶

Conclusion and future directions

In nociceptive and inflammatory pain, NGF activity and its interaction with trkA have been well characterized as important mediators of pain initiation and maintenance. In preclinical models of inflammatory and visceral pain, NGF sequestration and inhibition of trkA signaling have demonstrated a consistent analgesic effect. In contrast, the role played by NGF in the pathophysiology of neuropathic pain is less clear. Preclinical studies evaluating NGF and trkA antagonism exhibit a consistent benefit in the prevention of hyperalgesia and allodynia,^{14,28–34} yet pharmacotherapies targeting this pathway are yet to make it to market. Monoclonal antibodies have produced among the most promising new therapies for the treatment of cancers and immunological disorders, but their use in the treatment of pain has

been limited. Protein kinases, CGRP, and Nav1.7 have been investigated as potential targets; however, only cytokine- and NGF-directed monoclonal antibodies have reached clinical trials.^{6,77,78} To date, the systematic study of anti-NGF monoclonal antibodies in humans has yielded a mixed efficacy and safety record, and long-term follow-up studies are lacking, particularly in chronic disease indications. Even if anti-NGF monoclonal antibody-based treatments gain FDA clearance, the high costs of the therapy may outweigh its potential clinical value over existing treatment options. In rheumatoid arthritis, for instance, the price of therapies with monoclonal antibodies in the chronic setting can reach up to US\$24,000 per patient-year and the cost of tanezumab and fulranumab is more than an order of magnitude greater than other existing pain treatments.^{6,79} Furthermore, the authors believe that while several studies in OA patients have exhibited superior efficacy compared to active controls (oxycodone, naproxen, and celecoxib),^{43,45} and one study in patients with chronic mechanical LBP demonstrated superior efficacy to naproxen at 10 mg and 20 mg doses,⁵² additional large, pragmatic, comparative-effectiveness studies with long-term follow-up periods are needed across a variety of pain conditions and patient populations to fully assess the merits of anti-NGF therapy for chronic pain conditions.^{43,45,52,80} Due to the occurrence of rapidly progressive OA and joint destruction in clinical trials, it is also incumbent upon investigators to further delineate the risks of anti-NGF antibody therapeutics and improve their safety profile if anti-NGF therapy is to someday become a mainstay treatment for chronic pain. Nevertheless, in spite of its high cost, the relatively short-term follow-up periods in currently published trials, its uncertain adverse-effect profile, and its high cost, anti-NGF therapy may find a role as a short-term treatment in properly screened patients with refractory pain conditions.

Disclosure

The authors report no conflicts of interest in this work.

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