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Review

Nerve growth factor: an update on the science and therapy

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SUMMARY

Objective: Nerve growth factor (NGF) is a key regulator of nociceptive pain and thus appears to be an interesting target molecule for an innovative class of analgesic medication. We set out to review the principles of neurogenic inflammation and results of anti-NGF regimens in animal studies as well as clinical trials with patients with back pain and osteoarthritis (OA).
Design: We searched using Google Scholar Search and Pubmed as well as through conference reports for articles and abstracts related to NGF and clinical trials using anti-NGF regimens. We report on efficacy findings and adverse events (AEs) related to these agents in this review.
Results: We identified five full articles and eight abstract reports relating to anti-NGF agents studied for use in back pain and in OA.
Conclusions: Anti-NGF agents either alone or in combination with non-steroidal anti-inflammatory agents (NSAIDs) were more efficacious for the treatment of pain in a number of trials of knee and hip pain compared to NSAIDs alone. However, adverse effects that included rapidly progressive OA and joint replacement were more common in patients treated with anti-NGF and NSAIDs than either treatment alone. Anti-NGF treatment related neurologic symptoms including paresthesias, and potentially other types of adverse effects were usually transient but warrant additional investigation.

Introduction

Individuals with osteoarthritis (OA) and other rheumatic diseases, either inflammatory or degenerative, suffer from musculoskeletal pain. The long-term treatment of these disorders with mild analgesics, anti-inflammatory agents that block the cyclooxygenase pathways or more potent central acting narcotics is generally inadequate. In the past decade, new pathways for nociceptive pain induced by neurotrophins (NT) that activate peripheral sensory nerve pathways have been studied. Inhibitors of the NT nerve growth factor (NGF), have been developed and studied in both preclinical models and clinical studies of painful conditions. This review's goal is to provide a brief update on neurogenic inflammation, pain and in more detail the results and issues that have arisen from the clinical studies with inhibitors of NGF inhibitors.

Neurogenic inflammation, NGF and pain

Degenerative disorders such as many types of OA are a consequence of locally activated inflammation. Systemic diseases, on the other hand, are characterized by a variety of only partially characterized autoimmune stimuli, frequently with multi-organ pathology. Both local and systemic immunopathologies show similar patterns of activated proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), several interleukins and prostaglandins. These events may induce proliferation of different subsets of cellular populations with subsequent tissue lesions, loss of function and consequently reduced quality of life. Many of these events might be preceded by or coincide with increasing pain sensation. In rheumatology, painful disorders predominate in bone diseases and arthropathies such as rheumatoid arthritis and OA. Currently, it is unclear whether pain or inflammation, alone or together are the inciting events that result in chronic joint disease. Nevertheless, persistent peripheral nociceptor stimulation leads to a self-perpetuating activation of neurogenic inflammation with typical characteristics such as swelling, reddening and edema.

In the nervous system, several pain sensation neurotransmitters such as substance P (SP) or calcitonin gene-related peptide (CGRP) are able to induce peripheral inflammation at the site of peripheral nociceptors after antidromal axoplasmatic transport (review[1]).

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They may also induce the release of synovial fluid with neurogenic inflammation in experimental models[2]. Similarly, SP may also initiate or cause progression of arthritis in other animal studies[3]. These neurotransmitters thus show a dual mechanism of action consisting of action potential neurotransmission to the central nervous system (CNS) and at the same time induction or perpetuation of peripheral inflammation.

The expression of SP and CGRP can be upregulated by NGF[4]. This 13 kDa polypeptide belongs to a family of NT such as brain derived neurotrophic factor[5] and several other molecules including NT-3[6,7], NT-4/5[8,9] or NT-6. NGF was first described as a factor for embryonal growth and differentiation of neuronal crest sympathetic and sensory neurons. In adults, it regulates neuronal regeneration from injury and pain perception. Peripheral nociceptors express the tyrosine kinase (Trk) A receptor that is the major ligand for NGF. It binds to TrkA with high affinity and to p75 with low affinity. The former activates MAP kinases, phosphatidyl inositol-3 (PI3)-kinase and Ras. p75 signaling includes activation of Jun kinase, nuclear factor-kappaB (NF-kappaB) and others. Since TrkA is the major receptor for NGF it may be considered as perhaps one of the foremost receptors for pain modulation. TrkA expression is stimulated by NGF itself in basal forebrain in rats[10] suggesting that upregulation of NGF may result in amplification of pain sensation with hyperesthesia and allodynia. Conversely, proinflammatory neurotransmitters induce the overexpression of NGF which can result in a chronic self-perpetuating pain sensation mechanism[11]. In addition, NGF may also directly induce inflammation by activating chemotaxis in polymorphonuclear leukocytes[12] and by increasing vascular permeability[13]. NGF also mediates mechanical and thermal hyperesthesia upon systemic application in animals[14] and humans[15].

Animal studies – pain and effect of anti-NGF regimens

Experimental animal models of pain offer the advantage to study pathological mechanisms in more detail[16]. For example, peripheral joints with nociceptors, the spinal cord and the CNS are all available for concomitant analyses of neuropeptides. Moreover, animal strains allow a more uniform examination as compared to genetically variant humans. Tissue analyses of experimental diseases and animal behavior do not always correlate with the targeted human disease. Nevertheless, animal studies provide valuable insights into immunological events and thus may give insight into human diseases.

Similar to NGF-upregulation in human rheumatic diseases[17], animal studies show involvement of this molecule in experimental pain models. For example, NGF immunoreactivity was shown in dorsal spinal ganglia in experimental radiculopathy[18]. A similar overexpression of neuropeptides including NGF is found in animal models with experimentally induced arthritis[19–21] and OA in dogs[22]. These robust NGF-related reactions following pain and inflammation suggest that anti-NGF regimens may result in a reduction of pain perception. Indeed, several animal studies have shown impressive anti-inflammatory and analgesic effects[23–25]. In particular, pain behavior after partial ligation of the sciatic nerve was significantly reduced after intraperitoneal injection of anti-NGF antiserum[26]. Comparable results were found with a TrkA antagonist (ALE-0540) after ligation of lumbar nerve roots[27]. In an experimental fracture pain model with C57BL/6J mice, an anti-NGF antibody also showed significant pain reduction[28]. MNAC13 is an anti-TrkA monoclonal antibody that exhibited similar potent analgesic effects in formalin-evoked pain licking responses in mice[29]. One experimental OA model[30] indicates comparable analgesic effects of an anti-NGF regimen using the TrkA domain 5 (TrkAd5) protein, a soluble receptor with high affinity to NGF[31].

Anti-NGF agents for chronic low back pain (CLBP)

Several monoclonal antibodies directed against NGF have been tested or are undergoing trials for use in the context of CLBP. This application is predicated on the observation that treatment of CLBP generally involves multiple modalities and is often difficult to treat. Furthermore, the medications generally utilized (non-steroidal anti-inflammatory agents (NSAIDs) and opioids) may have very significant side effects including gastrointestinal, renal, cardiovascular or CNS toxicity with potentially lethal outcomes while at the same time there have been relatively few controlled comparative trials that have demonstrated the efficacy for long-term applications[32].

One randomized, double-blind controlled clinical trial evaluated the use of tanezumab, a humanized anti-NGF antibody in the context of CLBP in a population of adults with at least 3 months of non-radiculopathic back pain requiring regular analgesic medication[32]. A single intravenous infusion of tanezumab was compared with twice daily 500 mg of naproxen or placebo and study duration was 12 weeks. The primary efficacy outcome was the mean change from baseline to week 6 in average low back pain (LBP) intensity. Subjects in the tanezumab arm had greater decrease in average LBP intensity than subjects in the naproxen only arm ($P = 0.004$) or in the placebo arm ($P < 0.001$) at week 6 and a higher proportion of tanezumab-treated subjects reported “good” or “very good” LBP at 6 weeks in the Patient’s Global Assessment compared with naproxen and with placebo. Treatment related adverse events (AEs) were higher with tanezumab, the most common of which were arthralgia, headache, myalgia, and hyperesthesia that was dose dependent.

Another tanezumab study for chronic non-radiculopathic LBP was performed in which subjects were randomized to receiving tanezumab 20 mg, 10 mg or 5 mg every 8 weeks or naproxen 500 mg twice daily or placebo[33]. Tanezumab 20 mg and 10 mg both demonstrated superiority compared with both naproxen ($P = 0.006$ and $P = 0.035$ respectively) and with the placebo arm ($P < 0.001$ and $P < 0.001$ respectively) for the primary endpoint of change in average LBP intensity from baseline to week 16. The most common adverse event was paresthesia (ranging from 4.7 to 12.9% in the tanezumab groups vs 1.7% in the naproxen group and 2.2% in the placebo group), and there were no instances of osteonecrosis (ON) or total joint replacement.

A different monoclonal antibody against NGF, fulranumab (JNJ-42160443), has also been tested for efficacy for moderate to severe chronic LBP[34]. In this phase 2, multicenter double-blind trial, 389 subjects were randomized to receive fulranumab subcutaneously monthly in a variety of doses from 1 mg to 10 mg or placebo. The defined endpoint was change in average pain score from baseline to 12 weeks, and at no dose of fulranumab did the study drug differ from placebo ($P = 0.65$ for 10 mg dose). The most common AEs were diarrhea, headache, paresthesia, nasopharyngitis and upper respiratory tract infection.

Knee and hip OA

Monoclonal antibodies targeting NGF have also been undergoing testing for application in the treatment of pain in OA, particularly of the hip and knee. Pain in OA fluctuates over time and often presents as episodic severe pain against a background of chronic lower level pain, making treatment efficacy difficult to assess. A number of novel anti-NGF monoclonal antibody agents have been tested for this purpose, and a subset of trials have been reported either in journals or in abstract form over the last few years.

In 2010, Lane *et al.* reported the results of a phase 2 trial of tanezumab in 450 patients age 40–75 years with advanced OA of

the knee based on American College of Rheumatology (ACR) criteria who had not had an adequate response to nonopioid pain medications[35]. In this study, participants were randomized to a placebo arm or tanezumab 10, 25, 50, 100 or 200 μg per kilogram body weight which was delivered as infusions at week 0 and week 8 and with rescue medications of acetaminophen or tramadol allowed for the first 4 weeks and only acetaminophen allowed thereafter. The primary efficacy outcomes were change in walking pain and patient's global assessment of response to therapy averaged over weeks 1 through 16. All doses of tanezumab were superior to placebo in reduction of pain over 16 weeks (45–62% vs 22% for placebo; $P < 0.001$) and also in improvement by patient global assessment (29–47% vs 19% for placebo; $P < 0.001$). The most common reported AEs included headache, upper respiratory tract infection and paresthesia that was dose dependent.

An open-label extension of the Lane study was conducted to examine safety and effectiveness over a larger time-span[36]. Two hundred and eighty one patients all received 50 μg/kg of tanezumab at 8 week intervals up to a total of eight administrations. Patients who in the earlier study had been receiving lower doses of the study medication reported improvement in pain while those who had been receiving higher dose reported some worsening of their pain when switched to the 50 μg/kg. Mean reduction in visual analog scale pain from baseline was reported as 12.8 ± 1.78. The improvement in pain compared with the baseline of the earlier study appeared to persist through the 1 year of this extension study, without reported evidence of tolerance developing. The authors report that 7.5% of patients experienced a tanezumab-related adverse effect, that 2.8% experienced a serious adverse event (SAE) but that none of the SAEs were considered to be related to the study medication, and there were no deaths. The most common adverse effects were arthralgias ($n = 19$, 6.8%), back pain ($n = 17$, 6.0%) and headaches ($n = 16$, 5.7%), while hyperesthesia ($n = 1$, 0.4%), hypoesthesia ($n = 9$, 3.2%), peripheral neuropathy ($n = 1$, 0.4%), paresthesias ($n = 7$, 2.5%) and sensory disturbance ($n = 1$, 0.4%) were are all reported in 3.2% or less of the patients.

A phase 3 study has been conducted to evaluate tanezumab in three doses (2.5, 5, or 10 mg infused at 8 week intervals) for knee OA in comparison with placebo, with co-primary efficacy endpoints being change in Western Ontario and McMaster Universities OA Index (WOMAC) pain, physical function subscale scores and Patient's Global Assessment at week 16[37]. Patients were randomized and divided equally into the four arms. For all three efficacy endpoints, all three doses of tanezumab were superior to placebo, with what appears to be a dose–response pattern evident in the provided report. Mean change in WOMAC pain from baseline was approximately −2.4, −3.1, −3.2, −3.6 for placebo and tanezumab 2.5 mg, 5 mg, and 10 mg, respectively. AEs were reported in 55–60% of patients who received tanezumab compared with 48% in those receiving placebo, with more paresthesias (2.9–5.2% in tanezumab groups vs 1.7% in placebo) and hypoesthesias (2.9–4.1% in the tanezumab groups vs 1.2% in the placebo group) in the tanezumab group. Four patients received joint replacements, evenly divided across the study groups.

A randomized, double-blind study was conducted in Japan in 2008–2009 with 83 participants aged 44–73 years with knee OA[38]. Patients were randomized into five groups and received a single IV dose of tanezumab of 10 μg/kg, 25 μg/kg, 50 μg/kg, 100 μg/kg, 200 μg/kg or placebo. At 8 weeks post-infusion tanezumab 25 μg/kg, 100 μg/kg, 200 μg/kg showed improvement in index knee pain during walking over placebo (−18.5, −14.3, and −27.6, respectively). AEs occurred least frequently in the 25 μg/kg group with 26.7% experiencing AEs, while 100% of patients in the 200 μg/kg group experienced AEs. Seven patients experienced abnormal sensation, six of which were in the tanezumab groups. Three patients had severe AEs, none deemed to be related to the study medication.

A number of abstracts have also been published reporting anti-NGF antibody studies. In 2011 at the ACR Annual Conference, Fidelholtz and colleagues[39] reported that 610 patients with painful knee or hip OA who received one or two doses of tanezumab 10 or 5 mg or oxycodone 10–40 mg every 12 h or placebo were evaluated for WOMAC pain subscale. They found that both tanezumab doses ($P < 0.001$) but not oxycodone ($P = 0.700$) had greater improvement in pain compared with placebo at week 8, and that tanezumab was also superior to oxycodone in pain improvement ($P < 0.018$). There was also one patient with rapidly progressive OA (RPOA) and another with ON in the tanezumab groups (roughly 0.5%) as well as several joint replacements felt not to be related to the study.

Also in 2011, 604 patients with moderate to severe knee or hip OA already on diclofenac were enrolled into a randomized double-blind placebo controlled trial. The treatment groups were tanezumab at 2.5 mg, 5 mg, or 10 mg or placebo at 8 week intervals[40]. For all doses of tanezumab, WOMAC pain reduction was significantly greater for tanezumab plus diclofenac vs placebo plus diclofenac (−1.7 for placebo vs −2.1, −2.2, and −2.3 for tanezumab 2.5 mg, 5 mg, and 10 mg respectively, taken from figure). Six tanezumab-treated patients reported ON, but these diagnoses were not confirmed by an external adjudication committee due to insufficient radiographic information or because they were determined to be other diagnoses. Joint replacement due to possible ON, OA or arthralgia occurred in 2.8% ($n = 4$ subjects) of those receiving the highest dose of tanezumab and 0.7% ($n = 1$ subject) of those receiving placebo.

A different study from the same group compared efficacy of tanezumab with non-steroidal anti-inflammatory drugs in patients with hip or knee OA[41]. Patients were given naproxen 500 mg twice daily or celecoxib 100 mg twice daily or tanezumab 5 or 10 mg every 8 weeks or tanezumab in combination with either of the two NSAIDs. Tanezumab with NSAID or alone was associated with greater improvement in WOMAC pain than NSAID alone. WOMAC pain least squares mean change over 16 weeks was −1.44 for naproxen alone vs −1.88 for tanezumab 5 mg, −2.02 for tanezumab 10 mg, −2.13 for tanezumab 5 mg + naproxen, and −2.36 for tanezumab 10 mg + naproxen, all differences from placebo significant. WOMAC pain least squares mean change over 16 weeks was −1.43 for celecoxib alone vs −2.02 for tanezumab 5 mg, −2.05 for tanezumab 10 mg, −2.22 for tanezumab 5 mg + celecoxib, and −2.41 for tanezumab 10 mg + celecoxib, all differences from placebo significant. The authors observed increased risk for RPOA[42] in the hip or knee in the tanezumab group compared with the patients treated with NSAID alone.

A non-controlled but dose-blinded tanezumab study in patients with knee or hip OA was conducted to examine longer-term efficacy and safety[43]. 2142 patients received tanezumab 2.5 mg, 5 mg, or 10 mg every 8 weeks for up to 80 weeks. Patients who received all three doses of tanezumab experienced WOMAC pain mean change from baseline of approximately −4 by week 4 after the first infusion (from figure in abstract). Patients were reported to have maintenance of WOMAC pain relief over the extended period. 187 patients experienced joint replacement at a greater rate in the patients who also took NSAIDs (all cause joint replacement frequency was 5.2% in those not taking NSAIDs vs 13.0% in those who took NSAIDs).

Fulranumab was also tested for treatment of moderate to severe knee or hip OA pain[44]. Patients ($n = 466$) were given dosages of 1 mg or 3 mg every 4 weeks or 3 mg, 6 mg, or 10 mg every 8 weeks or placebo and were evaluated at the 12 weeks for average pain. Fulranumab was associated with significantly greater pain reduction

than placebo in the 10 mg every 8 weeks (between-group difference in least square means −0.8, 95% CI: −1.49, −0.08), 6 mg every 8 weeks (−0.8, 95% CI: −1.49, −0.08), and 3 mg every 4 week groups (−1.3, 95% CI: −1.97, −0.56). The most common AEs were paresthesia (7% overall in fulranumab groups vs 3% for placebo), headache (6% overall vs 4% placebo), hypoesthesia (4% overall vs 1% in placebo), nasopharyngitis (5% overall vs 1% placebo) and arthralgia (5% overall vs 8% placebo).

Regulatory agency concerns

In 2010, the Federal Food and Drug Administration (FDA) suspended clinical trials because of 492 suspected cases of ON observed in trials conducted by Pfizer, Regeneron and Janssen. These cases were observed in patients using NGF-antagonists alone or with NSAIDs, suggesting that the significantly greater analgesic effect of two separate classes of drugs prompted patients to permit increased joint load lacking the usual pain that would limit joint stress. The observations about AEs in tanezumab studies prompted Hochberg and colleagues to report on the process and results of adjudication of these events[45]. They found 282 joints to review and classified them into categories of ON, RPOA, normally progressive OA, not enough information to distinguish or other joint condition. Ultimately they identified two joints with ON, 71 with RPOA, 142 with normal progression, and 67 in the other categories. They found a significant dose–response relationship between incident RPOA and increasing dose of tanezumab, which was greater when tanezumab was given in combination with NSAIDs. A detailed benefit–risk calculation conducted by the FDA included considerations such as the imminent need for new and better tolerated analgesic drugs that do not share side effects that are observed with NSAIDs or opioids. Based on these findings and the apparent low incidence of ON, the FDA recommended reinitiating clinical studies in March 2012.

Current plan

Clinical trials will now resume with specific consideration for abnormal joint side effects. The study protocols that are being considered require a careful documentation of baseline clinical and radiographic findings of OA especially of the larger joints of the lower extremities. Baseline X-rays of both the index joints and other large weight bearing joints should be obtained upon entry into the clinical study to identify potential joint pathology in the absence of clinical involvement. Continuous clinical evaluations of the joint to include mobility, swelling or increased pain are warranted to identify developing RPOA. Separate magnetic resonance imaging diagnostics will also be important to consider in cases of unexpected joint pain or swelling. Additional imaging techniques such as bone scintigraphy may also be considered[46]. Furthermore, the separate study of different subsets of OA such as in obese vs non-obese patients, hand OA or post-traumatic and/or malalignment OA may provide valuable insights not only for the underlying individual pathophysiology but also for individual response rates. In addition to potential side effects involving the joint anatomy, several other organ systems have to be considered (review[47]). NGF is a pleiotrophic molecule that regulates a variety of metabolic pathways and organ functions. These include the CNS, the peripheral nervous system, wound healing, neoplastic diseases and immunosuppression. NGF-antagonists may have an impact on all of these organ systems although clinical trials thus far have not shown substantial signals. One may also speculate that inhibiting pain through anti-NGF treatment may result in increased cartilage degradation due to overuse of joints, and this should be considered going forward. Post marketing strategies should consider registries for large patient cohorts similar to those with other biologic regimens in rheumatology. It is possible that anti-NGF therapies may move into clinical practice and find a place in the treatment of OA pain in the future, and careful preparation for widespread use of these agents will be increasingly important.

Conclusion

In the light of expanding aging populations with increasing incidences of OA and CLBP, novel treatment regimens are warranted that do not share the same side effects as NSAIDs or opioids. The selective inhibition of NGF as a key regulator of chronic pain conditions shows promising results with potentially tolerable AEs. However, current and future studies will have to appreciate the pleiotropism of NGF with appropriate safety measures.

Author contributions

Concept and design: BLW, MFS, NEL.
Collection and assembly of data: BLW, MFS, NEL.
Preparation of manuscript: BLW, MFS, NEL.

Competing interests

BLW has received research funding within the last year from Pfizer, Inc. NEL has no competing interests in the last year. MFS has served on a Pfizer board last year.

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