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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