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SERVICES

Technology Assessment

My responsibilities were:

-  Research background and technical information
-  Determine product viability
-  Write 25-page report
-  Create Tables & Figures

Partial Text
WRITING SAMPLE

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CHRONIC PAIN THERAPY

Emerging Role of RN624 (tanezumab) for Pain Management

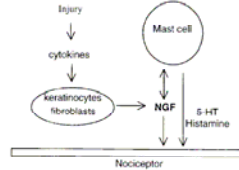
Most pain-relieving agents work by acting on receptors found in the central and peripheral nervous system. Opioid drugs block pain by locking onto opioid receptors in the brain. Other drugs, such as NSAIDs, control pain outside the brain by inhibiting prostaglandins, which stimulate nerves at the site of injury causing inflammation. COX2 inhibitors block cyclooxygenase-2 by impeding the production of prostaglandins. RN624 is a Nerve Growth Factor (NGF)-capturing agent that attenuates pain by binding to NGF.

NGF is a target-derived survival factor that plays an important role in human development. NGF also plays a critical role in the regulation of sensory neuron properties in inflammation and neuropathic states, as demonstrated in animal models. Experimental and clinical studies have allowed us to conclude:

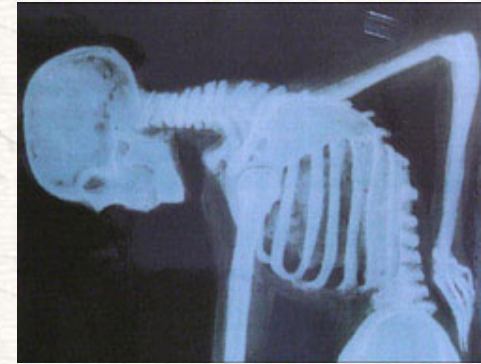
1. NGF levels are elevated in injury, inflammation and chronic pain states
2. Administration of NGF provokes pain and hyperalgesia
3. Inhibition of NGF function reduces pain and hyperalgesia in animal models
4. Genetic disorders of pain perception are caused by mutations in the genes that encode trkA and NGF

A predominance of NGF caused by the action of pro-inflammatory cytokines induces pain and hyperalgesia. Nociceptive action of NGF is dependent on trkA receptors, which are expressed on neurons and dorsal root ganglia. Antibody-mediated blockade has been shown to attenuate NGF-induced excitability in pre-clinical trials. NGF also causes pain by sensitizing TRPV1, a cation channel which serves as a molecular detector for noxious heat and extracellular acidification occurring in tissue inflammation. In addition, NGF triggers changes in gene expression in nociceptors sensitizing neurons to activation. Lastly, NGF sensitizes mast cells to release other pain mediators creating a positive feedback loop producing continual pain responses.

Role of NGF in Inflammation



Schematic diagram outlining the relationship of mast cells, nociceptors, and NGF as well as how this system is activated as a consequence of peripheral injury. Skin injury leads to release of cytokines, such as tumor necrosis factor- α and IL-1 β , which activate cells, such as keratinocytes and fibroblasts, to release NGF. The NGF can activate nociceptors directly but, in addition, can cause mast cells to degranulate, their products including 5-HT, histamine, and NGF. This endogenous source of NGF seems to be more potent than exogenous NGF in sensitizing nociceptors (see text for further details).



In order to prevent the activation of trkA by NGF effective blockade must occur. There are three mechanisms of action to inhibit activation of trkA. The first is by using a NGF-capturing agent. Other means are NGF-binding site antagonism and trkA antagonism. As a NGF-capturing agent, RN624 provides blockade of trkA, thus attenuating pain.

Beneficial Characteristics of RN624

RN624 is a humanized anti-NGF monoclonal antibody (MAb) currently in Phase 2 trials. Antibodies like this have exquisite specificity of target recognition and thus generate highly selective outcomes following systemic administration. Humanization of the murine IgG precursor provides an advantage over strictly murine-based antibody production. Murine antibodies are very similar to human ones; however the human immune system recognizes mouse antibodies as foreign the human patient mounts an immune response against them, producing HAMA (human anti-mouse antibodies). These not only cause the therapeutic antibodies to be quickly eliminated from the host, but also form immune complexes that cause damage to the eyes.

Monoclonal antibodies are typically given intravenously and the side effects are usually fairly mild and are often related to an allergic-type reaction. If that does occur, it is often while the drug is first being given. Possible side effects (not yet clinically determined for RN624) can include:

- Fever
- Chills
- Weakness
- Headache
- Nausea
- Vomiting
- Diarrhea
- Low blood pressure
- Rashes

Some MABs also have effects that are specific to the antigens they target. Phase 3 trials will determine if RN624 demonstrates any of these effects.

RN624 is a highly selective, and potent molecule with attractive pharmacokinetic properties. It has picomolar affinity being effective in animal models of chronic arthritic pain with an ED₅₀ of ~10 mg kg⁻¹. Its half-life is several days with a low clearance and minimal volume of distribution. Due to a mechanism of extravasation, the antibody preferentially distributes into inflamed tissues providing a unique advantage over small-molecule drugs.

