Existing analgesics fail to provide adequate pain relief in a significant proportion of patients complaining of chronic pain. Furthermore, their use is limited by tolerability and safety concerns. Thus, there is a huge unmet need for effective and safe innovative painkillers. Considering the major role of nerve growth factor (NGF) in the generation and maintenance of a wide range of pain states, the issue is whether anti-NGF biologics under development might offer such an opportunity.

Thanks to marked advances in the understanding of pathophysiological mechanisms underlying chronic pain states, numerous potentially important targets for developing novel painkillers have been identified over the past two decades. Unfortunately, new small chemical molecules acting on neurotransmitters (e.g., adenosine triphosphate, bradykinin, and various chemokines) or receptors (e.g., purinergic and vanilloid receptors) involved in pain processing produced rather disappointing results, and none has yet been approved for clinical use.1

Interestingly, biologics have emerged as an attractive alternative to chemical molecules. In this respect, monoclonal antibodies (mAbs) appear as a particularly appropriate option in view of their usual high-affinity and specificity for a predetermined ligand.1 Accordingly, mAbs may be virtually devoid of any off-target untoward effects. Owing to their protein nature, mAbs must be administered parenterally. However, they can be designed to produce long elimination half-lives, thereby allowing infrequent dosing. A more relevant feature is the poor capacity of mAbs to cross the blood-brain barrier as well as cell membranes. Therefore, they need to be directed against targets that are accessible in extracellular spaces. This condition is fulfilled by specific cytokines implicated in the pathogenesis of a variety of inflammatory rheumatic diseases. In fact, available mAbs that inhibit the activity of tumor necrosis factor-α, interleukin-1 or interleukin-6, do produce effective analgesia in patients with rheumatoid arthritis, spondyloarthritis, and/or gouty arthritis. Whether these agents are efficacious in relieving noninflammatory pain is, however, questionable. Of note, results from clinical trials of interleukin-1 and tumor necrosis factor antagonists in osteoarthritis—in the pathophysiology of which both cytokines are involved—were negative.2

Because nerve growth factor (NGF), the founding member of the neurotrophin family, was shown to function as a key peripheral mediator in a wide range of pain states, it might represent a good target for developing innovative broadly acting analgesics.3

**Evidence for the role of nerve growth factor in pain states**

NGF functions as a soluble signaling protein that mediates its activity via binding to two distinct cell surface receptors: the common 75 kDa neurotrophin receptor (p75<sub>NTR</sub>), which binds all neurotrophins with similar low affinity, and the high-affinity NGF-specific tyrosine kinase receptor (TrkA).3

NGF was identified originally as a critical factor for the development and survival of sensory and sympathetic neurons in the developing nervous system. NGF is now recognized as a pleiotropic factor, which, among others, plays a major role in the generation and maintenance of both nociceptive and neuropathic pain. This is supported by several lines of evidence.3,4 First, local or systemic administration of small doses of NGF provoked long-lasting hyperalgesia and pain in animals and humans alike. Second, elevated concentrations of NGF were found in damaged peripheral tissues, notably those associated with inflammation, in animals as well as in the synovial fluid from patients with inflammatory or degenerative arthritis. More generally, levels of NGF were reported to be increased in the serum of patients with various forms of arthritis, cancer pain, and neuropathic pain conditions. Third, inhibition of NGF function markedly reduced pain perception and hyperalgesia in animal models of inflammatory arthritis and osteoarthritis as well as postoperative, neuropathic, and visceral pain. Finally, there were cases of congenital pain insensitivity syndromes in humans linked to genetic mutations in the genes encoding NGF or TrkA. This is in agreement with experimental data suggesting that NGF-induced nociception occurs, for the most part, via TrkA. Briefly, proinflammatory cytokines released in injured and inflamed tissues induce overexpression of NGF, which, in turn, decreases pain thresholds...
through TrkA-mediated sensitization of peripheral neurons. Furthermore, NGF binds to TrkA on non-neuronal cells, including macrophages and mast cells, thereby promoting the release of pain mediators and stimulating sensory neurons. Conversely, p75NTR may have a predominant role in neuropathic pain. These findings provided the rationale for the development of humanized anti-NGF mAbs. By capturing and sequestering free NGF, these biologics may disrupt ongoing pain signaling by preventing interactions between NGF and its receptors.3

Clinical efficacy of anti-nerve growth factor monoclonal antibodies in pain

Among anti-NGF mAbs that have entered clinical trials, tanezumab is at the most advanced stage of development (Table 1). These compounds were primarily investigated in patients with symptomatic osteoarthritis of the knee and/or hip. As compared with placebo, tanezumab 5 mg and 10 mg administered i.v. at eight-week intervals (Q8w) provided similar clinically meaningful and statistically significant improvements in pain and physical function.4 Moreover, tanezumab seemed superior to nonsteroidal anti-inflammatory drugs and oxycodone. Phase II placebo-controlled trials of fulranumab and fasinumab also generated positive results.4

Regarding patients with chronic nonspecific low back pain, tanezumab 10 mg and 20 mg Q8w produced greater improvements in pain and physical function than placebo or naproxen 1 g/day, whereas neither tanezumab 5 mg Q8w nor fulranumab (even at high doses) outperformed the placebo.4 Studies in neuropathic pain also generated mixed results.4 Data from early phase clinical trials suggested that anti-NGF mAbs may alleviate pain related to diabetic peripheral neuropathy.4 Conversely, negative results were reported in patients receiving fasinumab for acute sciatica because of nerve root compression. Moreover, fulranumab did not demonstrate analgesic efficacy in patients with either posttraumatic neuralgia or postherpetic neuralgia.4 However, a type II error might account for the disappointing findings in postherpetic neuralgia, because only 65 of 150 planned patients were actually enrolled in the study.4 Furthermore, tanezumab produced inconsistent efficacy data in two proof-of-concept trials of urologic chronic pelvic pain syndrome, a form of functional somatic pain syndrome.4 Finally, tanezumab did not meet the primary efficacy end point in a phase II trial of patients with painful bone metastases, but the full results have not yet been published.

In summary, available data suggest that anti-NGF mAbs are more effective in some pain conditions than in others. The reasons for these differences are unknown. They are probably multifactorial, and might result, in part, from differences in baseline NGF levels across pain conditions studied.

Safety issues for anti-nerve growth factor monoclonal antibodies

Anti-NGF mAbs were generally well-tolerated by patients enrolled in clinical trials, and study discontinuation rates because of adverse effects (AEs) were usually <5–10%.4 Treatment-emergent AEs were similar across anti-NGF mAbs, thus being

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**Table 1** Efficacy results of published clinical trials of anti-nerve growth factor monoclonal antibodies in chronic pain conditions

<table>
<thead>
<tr>
<th>Pain condition</th>
<th>Anti-NGF mAb generic name</th>
<th>Phase</th>
<th>Main efficacy findings</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>OA of the knee/hip</td>
<td>TNZ</td>
<td>II &amp; III</td>
<td>More effective than placebo, NSAIDs, and oxycodone</td>
<td>TNZ 5 mg Q8w = 10 mg Q8w &gt;2.5 mg Q8w</td>
</tr>
<tr>
<td></td>
<td>FUL</td>
<td>II</td>
<td>More effective than placebo</td>
<td>Superiority shown for FUL 3 mg Q4w, and 6 mg or 10 mg Q8w</td>
</tr>
<tr>
<td></td>
<td>Fasimunab</td>
<td>II</td>
<td>More effective than placebo</td>
<td>Positive dose-response</td>
</tr>
<tr>
<td>LBP</td>
<td>TNZ</td>
<td>II</td>
<td>More effective than placebo and naproxen</td>
<td>TNZ 10 mg Q8w = 20 mg Q4w; TNZ 5 mg Q8w: no proven efficacy</td>
</tr>
<tr>
<td></td>
<td>FUL</td>
<td>II</td>
<td>No statistically significant difference vs. placebo</td>
<td>FUL doses ranged from 1 mg to 10 mg, Q4w</td>
</tr>
<tr>
<td>Diabetic neuropathy</td>
<td>TNZ</td>
<td>Iia</td>
<td>Superior to placebo</td>
<td>Single dose of TNZ 20 mg</td>
</tr>
<tr>
<td></td>
<td>FUL</td>
<td>II</td>
<td>Superior to placebo</td>
<td>FUL 10 mg Q4w &gt;3 mg Q4w &gt;1 mg Q4w</td>
</tr>
<tr>
<td>Postherpetic neuralgia</td>
<td>FUL</td>
<td>II</td>
<td>No statistically significant difference vs. placebo</td>
<td>FUL 1 mg, 3 mg or 10 mg Q4w (type II error?)</td>
</tr>
<tr>
<td>Posttraumatic neuralgia</td>
<td>FUL</td>
<td>II</td>
<td>No statistically significant difference vs. placebo</td>
<td>FUL 1 mg, 3 mg or 10 mg Q4w</td>
</tr>
<tr>
<td>Interstitial cystitis</td>
<td>TNZ</td>
<td>Iia</td>
<td>Superior to placebo</td>
<td>Single dose of TNZ 200 µg/kg</td>
</tr>
<tr>
<td>CP/CPPS</td>
<td>TNZ</td>
<td>Iia</td>
<td>No statistically significant difference vs. placebo</td>
<td>Single dose of TNZ 20 mg</td>
</tr>
</tbody>
</table>

CP, chronic prostatitis; CPPS, chronic pelvic pain syndrome; FUL, fulranumab; LBP, chronic nonspecific low back pain; mAb, monoclonal antibody; NGF, nerve growth factor; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; Q4w, every 4 weeks; Q8w, every 8 weeks; TNZ, tanezumab.
suggestive of “class-specific effects.” Peripheral edema, arthralgia, and pain in the extremities were among the most common AEs reported. Special attention was paid to neurological AEs—because of the possible role of NGF for the maintenance of adult neurons—and joint failure requiring total joint replacement—an unpredicted safety signal that led the US Food and Drug Administration to place the noncancer pain-related trials of NGF antagonists on clinical hold in 2010.

Cutaneous sensory symptoms (hypoesthesia, paraesthesia, or, in some instances, burning pain or allodynia) occurred in ≥5–10% of anti-NGF mAb-treated patients, and tended to be dose-related. They were generally transient and resolved without sequelae. Nevertheless, some patients experienced abnormal peripheral sensation for several months, and others were diagnosed with new or worsened peripheral neuropathies, including focal mononeuropathy (predominantly carpal tunnel syndrome) and, more rarely, radiculopathy and peripheral polyneuropathy. One possible explanation is that anti-NGF mAbs merely induced functional alterations of peripheral nerves that exacerbated preexisting subclinical or symptomatic neuropathies. However, it cannot be excluded that NGF inhibition might be associated with irreversible structural neurotoxic effects.

Furthermore, patients given anti-NGF mAbs had a dose-dependent increased risk for developing rapidly destructive arthropathies. The risk was greater with longer duration of anti-NGF exposure and even greater when nonsteroidal anti-inflammatory drugs were used concurrently. Both weight-bearing and non-weight-bearing joints were affected, as were joints with no-to-minimal osteoarthritis. The mechanism that triggered such AEs is still unclear. However, it must be kept in mind that NGF was reported to contribute to processes involved in tissue homeostasis and repair. NGF inhibition might thereby impair bone remodeling and compromise joint integrity.

**Concluding remarks**

Results from clinical trials of anti-NGF mAbs were somewhat disappointing in light of the promising findings from preclinical studies. First, pain disorders displayed significant differences in their responsiveness to these agents. So far, the most consistent efficacy data were obtained in patients with osteoarthritis. Second, clinical studies raised safety concerns, including an increased risk of joint failure and neurological disorders. These untoward effects are unlikely because of drug off-target effects. Instead, they might be a consequence of the pleiotropic biological activities of NFG. Finally, patients treated with humanized anti-NGF mAbs may develop antidrug antibodies, and these may alter the pharmacokinetics of the drug and result in a gradual loss of response over time.

Although pharmaceutical companies may have been allowed to resume clinical trials of anti-NGF mAbs, particularly in pain states for which no satisfactory therapy exists, under the condition of implementing adequate risk minimization measures, it is questionable whether these biologics might lead to a new era in pain therapy. This does not mean, however, that ongoing and future research efforts for discovering novel analgesics should give up the mAb approach. Interestingly, it was recently reported that an mAb targeting the voltage-gated sodium channel Na,1.7, the channel subtype critical for pain sensation, effectively suppressed inflammatory and neuropathic pain in mice. The future of biologics in pain management is, of course, unforeseeable, but the game is not over yet.

**CONFLICT OF INTEREST**

B.B. received consulting fees from Pfizer, Lilly, and Janssen Research & Development. M.K. has no conflicts to disclose.

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