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Editorial

Targeting nerve growth factor to relieve pain from osteoarthritis: What can we expect?

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National and international recommendations about the management of osteoarthritis emphasize the need for combining pharmacological and non-pharmacological treatments [1]. They have the major advantage of underlining the importance of physical activity, physiotherapy, and weight loss to relieve the symptoms, instead of relying solely on medications or intra-articular treatments. Nevertheless, medications have a role to play, as acknowledged in the recommendations. However, the spectrum of available drugs has narrowed substantially in recent years. Some drugs, such as dextropropoxyphène–acetaminophen have been taken off the market after they were discovered to induce serious adverse events. Others have seen restrictions to their indications: for instance, a history of cardiovascular disease is now an absolute or relative contraindication to nonsteroidal anti-inflammatory drug (NSAID) therapy. For other medications, including symptomatic slow-acting drugs for osteoarthritis and hyaluronic acid, absence of reimbursement by the statutory health insurance system is a limitation to prescription in France. Acetaminophen, the first-line medication in all recommendations until now, has failed to show evidence of clinically relevant efficacy in well-designed trials and is suspected to induce rare but serious adverse events previously thought to occur only with NSAIDs. Given these new data, the risk/benefit ratio of acetaminophen as a treatment for osteoarthritis is now deemed unsatisfactory, challenging the use of this drug as a first-line treatment [2,3]. A more serious trend is the recent opioid epidemic that has caused numerous deaths in the US in patients who were initially prescribed opioids, often for pain from osteoarthritis, and subsequently developed an addiction to these drugs. Opioid dependency and the host of serious adverse events associated with it has caused hundreds of thousands of deaths in recent years, and there is no evidence that this epidemic is abating [4]. It comes therefore as no surprise that the medical community is putting considerable hope in the advent of a new class of analgesics that target nerve growth factor (NGF). Anti-NGF drugs are monoclonal antibodies and therefore belong to the vast family of biologics that have constituted a therapeutic breakthrough in other joint diseases. The Food and Drug Administration in the US has granted fast-track status to anti-NGF drugs, including anti-NGF antibodies and synthetic antagonists of the NGF receptor [5], in the hope of putting an end to the epidemic of opioid-related deaths, particularly as it has been criticized for having contributed to the expansion of opioid use [6,7]. Whether this considerable enthusiasm for anti-NGF drugs is warranted or constitutes an overreaction to a novel therapeutic approach at a time when the pharmacological treatment of osteoarthritis is struggling deserves careful evaluation.

NGF is a neuropeptide of the neurotrophin family whose role consists chiefly in regulating the growth, maintenance, proliferation, and survival of subsets of neurons [5]. NGF binds to the tropomyosin-related kinase-A (TrkA) receptors at the surface of sensory neurons [8]. This interaction amplifies pain – chiefly nociceptive pain – by enhancing the production of, and neuron sensitivity to, several neuromediators involved in pain, including substance P and calcitonin gene-regulated peptide [9]. The first trials in humans of anti-NGF antibodies were conducted over a decade ago [10]. The unusually long time from the first clinical trials to the initiation of pivotal Phase III trials is ascribable to the unexpected occurrence of serious adverse events during the development process. In 2010, rapid joint destruction, classified in some cases as osteonecrosis and usually requiring total joint replacement, was reported during anti-NGF therapy with a frequency of up to 3/100 patient-years [11,12]. The FDA immediately put all the ongoing trials on hold while experts analyzed the possible causes of this apparently paradoxical adverse effect. To date, no fully convincing explanation has been found. Hypotheses include neurogenic arthropathy, joint overuse allowed by pain relief, and abnormalities in subchondral bone metabolism. However, the vast majority of cases of rapid joint destruction occurred in patients who were taking both high-dose anti-NGF therapy and an NSAID. This fact allowed the clinical trials to resume thanks to the implementation of mitigation plans. In 2012, however, an animal study suggested possible adverse effects of anti-NGF therapy on the sympathetic nervous system. Further preclinical trials were therefore conducted. The results failed to confirm the suspicion and the clinical trials were again resumed. Today, two drugs are being evaluated in Phase III trials, tanezumab (Pfizer and Lilly) and fasinumab (Regeneron and Teva). Both are administered subcuta-

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neously, in a dosage of 2.5 or 5 mg every 8 weeks for tanezumab and 1 mg every 4 or 8 weeks for fasinumab. The main objective of these vast ongoing Phase III trials is to assess the safety profile. More specifically, the trials will seek to determine whether the risk-reduction strategy consisting in using a lower anti-NGF dosage than in earlier trials and contraindicating concomitant NSAID therapy is effective in ensuring treatment safety. Another reported adverse event is the occurrence in about 10% of patients of upper limb paresthesia, which may resemble carpal tunnel syndrome. This symptom resolves upon treatment discontinuation. Nevertheless, long-term studies, and post-marketing studies if the drugs proceed to licensing, will be needed to determine whether the occurrence of paresthesia limits treatment adherence, which is expected to be good given the administration by subcutaneous injection every 8 weeks. Finally, although not substantiated by data at present, one concern is that anti-NGF drugs might mask pain that serves as a useful warning sign, such as pain from coronary artery syndromes.

1. How effective are anti-NGF drugs?

The first Phase II study, published in 2010 in the *New England Journal of Medicine*, was conducted in patients who had analgesic-refractory pain due to osteoarthritis of the hip or knee [13]. The results were dramatic, with a far greater degree of pain relief compared to the maximum efficacy of standard analgesics. The effect size of up to 0.73 versus the placebo was clinically relevant. It is worth noting, however, that these somewhat remarkable results were obtained with anti-NGF dosages far above those currently recommended to maintain an acceptable risk/benefit ratio. Interestingly, a recent metaanalysis of both Phase II and Phase III studies has somewhat tempered our enthusiasm regarding the efficacy of anti-NGF drugs [14].

2. Do anti-NGF drugs hold potential for other rheumatic diseases?

The mechanism of action of anti-NGF drugs is sufficiently broad to support usefulness in other diseases responsible for pain. More specifically, anti-NGF drugs are at present the only analgesics that have shown clinically relevant efficacy in nonspecific low back pain [15]. The dosage needed to obtain pain relief will be higher than those recommended for knee or hip osteoarthritis. The articular tolerance of anti-NGF drugs injected at the spine will by carefully assessed in ongoing trials.

3. Persistent unknowns

Over 4 million patients in France have symptomatic knee or hip osteoarthritis, and millions suffer from low back pain [16]. Anti-NGF drugs carry a risk of potentially serious adverse events, and their cost is expected to reflect the considerable investment in innovation, research, and development that was needed to make them available. Consequently, identifying those patients most likely to benefit is a key priority. Possible target patient subsets may be patients younger than 50 years in whom the goal is to postpone joint replacement surgery; elderly patients who have contraindications to, or do not want, joint replacement surgery; and patients with responsive phenotypes that can be identified before starting the treatment. All these possibilities have been the focus of in-depth discussions. A detailed analysis of the available data from the thousands of patients already exposed to anti-NGF therapy is needed to assist clinicians in their treatment decisions.

In conclusion, the medical community should feel gratified to participate in the development of a novel class of analgesics designed to relieve chronic joint pain and perhaps also low back pain, which is currently among the leading causes of disability worldwide [17]. Nevertheless, evaluating the risk/benefit ratio of anti-NGF drugs remains challenging, as the long-term pivotal trials have not yet been completed. The results of these trials are indispensable to better assess the efficacy of anti-NGF drugs in the current dosages, which are lower by at least 50% than those used in the first trials, and to define the risk of rapid joint destruction when the risk-reduction strategy is followed. Clearly, the entire medical community is impatiently awaiting progress in the pharmacological management of chronic joint and low back pain. Anti-NGF drugs currently hold the most promise, and we can only hope that they will not disappoint.

Disclosure of interest

FB has financial ties to Pfizer, Lilly, Regeneron, Sanofi, Janssen, and Johnson & Johnson.

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