Current status of nerve growth factor antibodies for the treatment of osteoarthritis pain

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ABSTRACT
Blockade of nerve growth factor (NGF) with antibodies is a promising strategy for treatment of chronic pain associated with osteoarthritis (OA). This narrative review describes the current status of NGF-blockade for the treatment of OA pain. We summarise briefly current evidence for the efficacy and risks of anti-NGF blockade. Two anti-NGF antibodies, tanzezumab and fasinumab, are in active development, with tanzezumab close to completing Phase 3 trials in preparation for an application for approval for clinical use.

Osteoarthritis (OA) is a painful disease of the synovial joints, and frequently affects the knees, hips, hands, feet, and spine. Inadequately treated OA pain represents an enormous unmet medical need worldwide. The most recent update of the Global Burden of Disease figures (2013) estimated that 242 million people were living with symptomatic and activity-limiting OA of the hip and/or knee (1). While there presently are no therapeutic approaches that have been demonstrated to retard or reverse disease progression, palliative modalities are effective and therapy is focused on pain relief and maintenance of joint function. Non-steroidal anti-inflammatory drugs (NSAIDs) have been the mainstay of therapy for more than a century and provide durable relief for many patients. Nonetheless, a large number of OA patients are unable to take NSAIDs, either due to intolerable side effects or to potential toxicity related to age, renal, cardiac, or gastrointestinal conditions. Other analogues that are used include tramadol and opiates, but these substantially increase morbidity, especially among the elderly (2). More recently (2010), the centrally-acting serotonin and noradrenaline reuptake inhibitor, duloxetine, was approved for the treatment of musculoskeletal pain, including OA (3).

Notwithstanding these existing treatment options, inadequate pain relief remains a major problem for OA patients (4). As understanding of the pathophysiology of OA pain has progressed, it has become apparent that much of the refractory pain associated with OA may be of neurogenic origin or may be responsive to neutralising specific neurotransmitters (5, 6). Of the potential novel strategies for pain control in OA (7), clinical development is most advanced for strategies that target the neurotrophin, nerve growth factor (NGF). This narrative review provides a brief summary of the current status of NGF-blockade for the treatment of OA pain. We searched PubMed for the following terms: “osteoarthritis”, “pain”, “clinical trials”, “nerve growth factor”, “antibodies”, “symptoms”; papers published since 2015 were included. In addition, we searched www.clinicaltrials.gov for active and recently completed clinical trials for symptomatic OA testing anti-NGF antibodies.

In the early 1950s, Rita Levi-Montalbani and Stanley Cohen began describing NGF and its key role in the development of the nervous system, a discovery that earned them the 1986 Nobel Prize in Medicine (8). Forty years after its discovery, it was recognised that, in addition to its role as a growth factor for cells in the peripheral nervous system, NGF is a key mediator of acute and chronic pain. Different biological actions of NGF contribute to its proalgesic effects, including NGF-induced sensitisation of peripheral nociceptive terminals and NGF-induced sprouting of sensory nerves (9). Antagonism of NGF is therefore an attractive strategy for pain relief (10). Monoclonal antibodies can be used to inhibit the binding of NGF to its high-affinity cognate receptor, tropomyosin-related

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kinase (Trk)A, and thus block its biological activity. As a result, there was a vigorous effort by the pharmaceutical industry to develop humanised monoclonal antibodies that bind NGF with high specificity and affinity. These include tanezumab (Pfizer and Eli Lilly), fasinumab (Regeneron and Teva), and fulranumab (Janssen and Amgen). Of these, tanezumab has been the most widely studied, and formed the basis of the first large randomised double blind controlled trial of anti-NGF therapy for OA pain, which was published in 2010 and revealed dramatic pain relief among many study subjects (11). Although these findings produced initial optimism, further experience suggested that there was a high prevalence of rapidly progressive OA and osteonecrosis in non-target joints among subjects who had received anti-NGF treatment. Subsequently, the US Food and Drug Administration (FDA) imposed a hold on all clinical trials of NGF antagonists, which was subsequently extended because of the observation of autonomic nervous system toxicity in preclinical models (12). In 2015, the hold was lifted subject to the imposition of stringent monitoring, dose limitations, and enrolment restrictions, discussed below.

At the time of writing, Phase 3 trials of tanezumab in preparation for an application for approval for clinical use are close to completion. The FDA recently has granted Fast Track designation (a process designed to facilitate the development and expedite the review of new therapies to treat serious conditions and fill unmet medical needs) for this antibody for the treatment of OA pain and chronic low back pain. Phase 3 clinical trials of fasinumab (Regeneron/Teva) are ongoing, while fulranumab has been discontinued by Janssen (https://www.jnj.com/media-center/press-releases/janssen-announces-discontinued-offulranumab-phase-3-development-program-in-osteoarthritis-pain).

During the past two years, several systematic reviews (13-15) have concluded that, compared to placebo, blockade of NGF with targeted monoclonal antibodies yielded substantial improvement in pain and in function. Tanezumab, used at doses of 5 mg and 10 mg, was statistically significantly superior to the active comparators, NSAIDs or opiates, with standardised effect sizes of 0.22 to 0.24 (13, 16). Chen et al. reported that low dose (≤2.5 mg) tanezumab treatment had comparable efficacy to high dose, but with significantly fewer adverse effects (15). Since then, development of higher dose anti-NGF has been discontinued. It is important to note that whereas the data to-date strongly suggest that anti-NGF treatment has substantial pain palliative activity in OA, all reported trials have been funded by the pharmaceutical industry and there are no independently funded trials listed in www.clinicaltrials.gov nor are there independent data.

As noted above, in 2010, the US FDA placed a hold on all clinical trials involving anti-NGF therapy. This decision was based on reports of rapidly progressive OA and of osteonecrosis among patients who had received anti-NGF antibodies, including in non-target joints that were not known to have OA. As this was presumed to be a class effect, all anti-NGF agents were affected. A Pfizer-funded expert adjudication committee performed detailed reviews of the adverse events that were reported in clinical trials with tanezumab. The committee noted a dose-response relationship between rapidly progressive OA and osteonecrosis with doses of tanezumab between 2.5 and 10 mg (17). Therefore, when trials were resumed in 2015, they included a dose-restriction of maximum 5 mg. Subsequently, a similar dose-response relationship was identified with fasinumab doses between 3 and 9 mg (18, 19), and only lower doses are currently under investigation.

It should be noted that the incidence of osteonecrosis may be lower than initially thought. The adjudication committee could demonstrate unambiguous osteonecrosis in only two of the 86 reported osteonecrosis cases (although eight of those had insufficient information to distinguish primary osteonecrosis and the committee failed to reach consensus concerning another five) (20). It was also concluded that the risk of developing rapidly progressive OA appeared to be significantly higher when tanezumab was used in conjunction with NSAIDs, compared to tanezumab monotherapy (17, 20). Therefore, subsequent trials impose strict limits on NSAID use during exposure to anti-NGF therapy. As part of the risk mitigation strategy for the tanezumab trials, pre-enrolment radiographic imaging is performed in order to exclude patients with pre-existing shoulder, hip, and knee joint abnormalities, including subchondral insufficiency fracture, atrophic or hypotrophic OA, excessive malalignment of the knee, osteonecrosis, severe chondrocalcinosis, rheumatoid arthritis, systemic metabolic bone disease, tumours, fractures, and large cystic lesions (21). In addition, radiographic follow-up will be part of the trial design (21).

The mechanisms by which anti-NGF antibodies may promote structural joint damage are not understood. Few studies have tested the effects of NGF blockade in experimental models of OA. The data suggest that there may also be a risk for accelerated joint damage, but potential mechanisms were not (or only minimally) explored (22).

As clinical trials are ongoing and nearing completion, it will be important to assess the actual benefits and risks of anti-NGF therapy. Cost-effectiveness analyses suggest that pain relief provided by anti-NGF therapy is sufficiently significant that even a rate of rapidly progressive OA occurring in up to 10% of patients would not nullify the overall improvement in quality-adjusted life years (QALY) achieved (23), and that anti-NGF therapy could be cost effective at up to $400 per dose (23).

In conclusion, it appears that anti-NGF therapy offers great potential to palliate pain and function in patients who have severely symptomatic OA that is not responsive to conventional analgesics. Nonetheless, as there are clearly risks of significant adverse effects, it will be critical to identify patients who are most likely to benefit from this therapy, and perhaps more important, to recognise those patients at greatest risk of toxicity. Ongoing safety studies and post-marketing surveillance will be necessary to fully define these groups (24).
References
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