Tanezumab: Finally a Monoclonal Antibody for Pain Relief

Sir,

Nerve growth factor (NGF) is a neurotrophin that promotes the growth and differentiation of sensory and sympathetic ganglia. Inflammation and peripheral nerve injury lead to increased levels of NGF. NGF is also increased in all chronic nociceptive and neuropathic pain states which include all types of cancer and noncancer pain. NGF is produced as a response to any noxious stimuli that produce inflammatory cytokines such as interleukin-1 and tumor necrosis factor alpha.[1]

NGF binds to tropomyosin-related kinase A (trkA) which is expressed on the A-delta and C-fibers. NGF also binds to trkA on mast cells and releases histamine, serotonin, protons, and thereby starts a vicious cycle of inflammation.

Tanezumab is a humanized monoclonal IgG2 antibody that blocks NGF from activating trkA receptors on nociceptive neurons. The inhibition of NGF in acute and chronic painful states is a novel mechanism of action, unlike opioids and nonsteroidal anti-inflammatory drugs (NSAIDs). By inhibiting NGF, tanezumab interferes with pain signals produced by muscles, skin, and organs from reaching the spinal cord and brain. Clinical trials with tanezumab started in 2009 with doses of 10, 25, 50, 100, or 200 μg/kg on day 1 and day 56 (8 weeks).[2] However, in one of the Phase III trials, 16 patients required hip replacement which was thought due to rapidly progressing osteoarthritis and radiologically evident bone necrosis due to the drug. This brought a halt to the trial in June 2010 due to not clearly defined safe dose of tanezumab (https://www.clinicaltrials. gov/show/NCT00744471).

The drug was later studied extensively with close monitoring of adverse effects. Randomized, double-blind, placebo-controlled Phase III trial by Brown *et al*. compared tanezumab with placebo and found tanezumab to be superior in providing pain relief and improvement in physical function versus placebo in patients with painful hip arthritis.[3] The authors used 2.5 mg, 5 mg, and 10 mg of tanezumab IV every 8 weeks for 24 weeks versus trkA placebo. Paresthesia and hypoesthesia were common adverse effects in all groups while some patients also had neuropathy, peripheral edema, upper respiratory tract infection, pain in extremity, arthralgia, urinary tract infection, and headache more common in patients who received 10 mg dose. The study showed that the dose of 5 mg and 10 mg had good response compared to 2.5 mg but 10 mg group had the highest incidence of adverse events. In neuropathic pain, the levels of NGF and severity of pathology are complex. Bramson *et al*. evaluated efficacy and safety of tanezumab in two neuropathic pain conditions: diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN) with placebo in each condition.[4] They observed that tanezumab was effective in DPN, but in PHN, even the maximum dose of 200 μg/kg every 8 weeks was not very effective. The reason for this could be the different pathology leading to neuropathic pain in both syndromes. In diabetes, there is length-dependent neuropathy, i.e., the longest axons in peripheral nerve are affected which involves small fibers. In PHN, the peripheral nerve is damaged due to herpes zoster infection due to which pain is along the affected dermatomes.[5]

U. S. food and drug administration has granted fast track designation for tanezumab in patients with osteoarthritis and chronic low back pain who are refractory to conventional medications (https://www.pfizer.com/news/press-release/press-release-detail/pfizer_and_lilly_receive_fda_fast_track_designation_for_tanezumab). The advantages are single injection every 8 weeks with minimal adverse effects. However, the cost of medication could be the limiting factor for its use. However, the drug is devoid of adverse effects such as constipation, respiratory depression, tolerance, and dependence like with opioids and has no cardiovascular or renal toxicity as observed with NSAIDs. Moreover, the dose comes once in 56 days or 8 weeks.

Tanezumab has equivocal efficacy when administered subcutaneously. This could reduce the cost further as injection can be taken by the patient at home without visiting the hospital or health-care provider.

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Conflicts of interest

There are no conflicts of interest.

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