EDITORIAL

Tanezumab for Painful Osteoarthritis

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Osteoarthritis (OA) is a painful, disabling condition that arises from damage to cartilage, synovium, subchondral bone, and other joint structures. An estimated 300 million people worldwide have OA,[1] including 30 million individuals in the United States,[2] of whom more than 14 million have symptomatic, radiographically documented knee OA.[3] Despite the enormous prevalence, cost, and disability associated with OA, no treatments are available to slow or reverse the inexorable destruction of joint structures that underlie the pain and disability of OA (although several agents are in various stages of evaluation, including strontium ranelate, sprifermin, and others).[4] Thus, the primary objectives of contemporary OA therapy have been to control pain and improve physical functional status.

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A range of medications are used to address the pain of OA, including nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and opioids, along with medications that modify central sensitization of pain including gabapentin and duloxetine. Each of these agents has important toxicities or limitations in efficacy, prompting interest in the identification of new agents (especially nonopioids) that are effective in managing the pain of OA.

Clinicians and investigators focused on OA therapeutics have been especially intrigued by nerve growth factor, a protein discovered in 1956 that is involved in the proliferation and maintenance of sensory neurons. Tanezumab, a humanized monoclonal antibody directed to nerve growth factor, has been shown to be effective in reducing pain associated with OA of the knee and hip as well as low back pain.[5-9] Subcutaneous tanezumab therapy also may be a cost-effective treatment for knee OA, depending on its price.[10]

However, in OA trials, tanezumab-treated patients have had higher risks of rapidly progressive OA and total joint replacement than patients treated with comparator medications or placebo.[7,11] Rapidly progressive OA has been defined as progression in joint space narrowing by more than 1 mm in 1 year (rapidly progressive OA type 1) or damage to bony structures not normally seen in advanced OA (rapidly progressive OA type 2).[11] While the mechanisms linking tanezumab to rapidly progressive OA and total joint replacement have not been defined definitively, investigators hypothesize that these complications arise because with reductions in pain, patients bear increasing loads on damaged joints. In essence, then, the analgesic efficacy of tanezumab may be the reason for its most important toxicity. Analyses from earlier trials suggested that rapidly progressive OA and total joint replacement occurred more frequently in patients treated concomitantly with tanezumab and NSAIDs than in those treated with tanezumab without NSAIDs.[11] Thus, in subsequent trials, tanezumab-treated patients have not been permitted to receive NSAIDs, and those with lesions, such as subchondral insufficiency fractures or avascular necrosis, which might be precursors to rapidly progressive OA, have been excluded. Also, reviews of the cases of rapidly progressive OA and total joint replacement occurring in tanezumab trials indicate that 44% of these events occurred in nonindex joints (joints other than the one that prompted the patient to seek care).[11] This is an important finding: A patient who selects tanezumab to reduce pain primarily in one index joint, is at risk for symptomatic progression of OA both at that joint and, potentially, others.

The trial by Schnitzer et al[12] reported in this issue of *JAMA* includes several of the design features intended to reduce the incidence of rapidly progressive OA and total joint replacement associated with tanezumab. These include moderate dosing, no concomitant use of NSAIDs, and pretrial screening to exclude persons with avascular necrosis or subchondral insufficiency fracture.[12] The investigators enrolled 698 patients with hip or knee OA and pain and function scores of 5 or greater on the 11-point Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), with presence of osteophytes on radiographs (Kellgren-Lawrence grade ≥2). Two did not meet eligibility criteria after randomization and 696 patients were randomized to receive 1 of 3 regimens, all delivered by subcutaneous injection: placebo at weeks 1 and 8 (232 patients); tanezumab, 2.5 mg, at weeks 1 and 8 (231 patients); and tanezumab, 2.5 mg at week 1 and 5 mg at week 8 (233 patients). Intermittent acetaminophen (paracetamol) was permitted as a rescue medication.

All 3 groups experienced marked pain relief from baseline to week 16, with greater relief in the tanezumab-treated patients. For example, 69% (321 of 464) of the tanezumab-treated patients improved by more than 30% in WOMAC Pain between baseline and 16 weeks compared with 55% (127 of 232) of placebo-treated patients. Importantly, however, the tanezumab-treated patients received more total joint replacements in the 40-week observation period: 16 of 233 (6.9%) in the tanezumab, 2.5/5.0 mg, group; 8 of 231 (3.5%) in the tanezumab, 2.5 mg, group; and 4 of 232 (1.7%) in the placebo group. These differences were statistically significant and suggest a dose-related increased frequency of total joint replacement in tanezumab-treated patients. Twenty-six of the 28 joint replacements (93%) involved the index joint.

The analgesic effect of tanezumab in this study is consistent with other single studies and meta-analyses of tanezumab

for OA, which have demonstrated more effective pain relief compared with placebo and with NSAID in the management of OA-related pain.[6-9,13] Studies that followed up patients for several months or longer have documented, as did Schnitzer et al,[12] the increased risk of total joint replacement or rapidly progressive OA.

Of note, in April 2019, Pfizer and Eli Lilly provided a press release summarizing a trial of 3021 patients with hip or knee OA randomized 1:1:1 to receive either tanezumab, 2.5 mg, every 8 weeks; tanezumab, 5.0 mg, every 8 weeks; or an NSAID daily.[14] These treatments were provided for 56 weeks and the investigators followed up the patients for an additional 24 weeks to achieve 80-week follow-up. Tanezumab-treated patients did not receive NSAIDs. The 5-mg dose of tanezumab was more effective than NSAID for pain relief and functional status improvement. The incidence of the composite adverse joint safety outcome (primarily rapidly progressive OA; also, osteonecrosis and fracture) was 7.1% in the tanezumab, 5 mg, group; 3.8% in the tanezumab, 2.5 mg, group; and 1.5% in the NSAID group. Similarly, total joint replacement occurred in 8.0% in the tanezumab, 5 mg, group; 5.3% in the tanezumab, 2.5 mg, group; and 2.6% in the NSAID group. Thus, this study, like that of Schnitzer and colleagues, showed that tanezumab is an effective analgesic for OA but is associated with higher frequency of rapidly progressive OA and total joint replacement.

Total joint replacement is a decision and not a pathoanatomic state. Many factors influence the decision to undergo total joint replacement aside from pain and radiographic severity. Thus, total joint replacement has been recognized as an imperfect but reasonable proxy for advanced symptomatic, radiographic OA. In addition, the similar pattern of associations between tanezumab and rapidly progressive OA and between tanezumab and total joint replacement reinforces the conclusion that tanezumab is associated with symptomatic OA progression.

The question that emerges from these studies is whether the analgesic benefits of tanezumab merit the potential damage to the joint and attendant risk of rapidly progressive OA and total joint replacement. If the medication is approved for clinical use in OA, patients and physicians will need to discuss these risks and benefits carefully. Patients considering this therapy will need to accept the possibility that tanezumab has the potential to hasten symptomatic OA progression and consideration of total joint replacement. For those patients at high risk for total joint replacement–related complications and those with strong preferences to avoid total joint replacement at all costs, tanezumab would not be a wise choice. Patients willing to accept the risk of total joint replacement in exchange for a greater probability of pain reduction than afforded by other available therapies would appear to be acceptable candidates for tanezumab. Additional data on the factors associated with use of total joint replacement among patients using tanezumab for OA would help with these decisions.

It could be argued that the risks of rapidly progressive OA and total joint replacement are too high for policy makers to permit entry of tanezumab into the market for advanced, symptomatic OA. However, given the prevalence and disability burden of OA, and the paucity of effective alternatives, it would be reasonable to allow patients and physicians to make these decisions together. If this agent enters the market, it will be essential for physicians to educate themselves and their patients about the short- and long-term benefits and potential harms of tanezumab. It would be reasonable for the manufacturers that market tanezumab to fund the development of high-quality educational materials to assist in this effort, and essential for the content of these materials to be developed independently by physician and patient groups. In the United States, the Food and Drug Administration has authority to require a Risk Evaluation and Mitigation Strategy for medications that pose serious safety concerns.[15] While a Risk Evaluation and Mitigation Strategy does not guarantee safe and appropriate prescribing,[16] it can impose specific requirements, such as trainings or certifications, to ensure that prescribers and patients are well informed. Thus, options exist that may mitigate risk while providing patients with effective analgesia to address the pain and attendant functional limitation of advanced, symptomatic OA.

ARTICLE INFORMATION

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