HHS Public Access

Author manuscript

Osteoarthritis Cartilage. Author manuscript; available in PMC 2020 November 01.

Published in final edited form as:

Osteoarthritis Cartilage. 2019 November ; 27(11): 1575–1577. doi:10.1016/j.joca.2019.07.013.

A Tale of Two TrkA Inhibitor Trials: Same Target, Divergent Results

DA. Walsh[*],

Pain Centre Versus Arthritis, and NIHR Nottingham Biomedical Research Centre, Academic Rheumatology, University of Nottingham.

T. Neogi

Section of Rheumatology, Boston University School of Medicine

Keywords

Osteoarthritis; pain; nerve growth factor; TrkA inhibitor; clinical trial

Nerve growth factor (NGF), a neurotrophin involved in the development of the nervous system, plays a key role in pain by sensitizing peripheral nociceptors following tissue injury or inflammation. This peripheral sensitization by NGF is mediated through binding to the high-affinity receptor tropomyosin-related kinase (Trk)A localized to peptidergic sensory nerves.[1] The NGF-TrkA complex is internalized and transported to the dorsal root ganglion, where it increases TRPV1 phosphorylation and the expression and release of neuropeptides including substance P and calcitonin gene-related peptide. Upregulated brain-derived neurotrophic factor (BDNF), induced by NGF and released in the spinal cord, might also contribute to central sensitization. NGF also binds low affinity p75 receptors, although the biological role of p75 is incompletely understood. Two other Trk receptors, TrkB and TrkC, have low affinity for NGF, and are predominantly localized in the central nervous system. However, TrkB and its preferred ligand BDNF have recently been implicated in OA pain mechanisms within the joint.[2]

NGF's role in human OA pain is strongly supported by positive results in clinical trials of each of several monoclonal antibodies which specifically block NGF. Tanezumab and fasinumab are currently in Phase 3 development for management of osteoarthritis (OA) and chronic low back pain. It is in this context that two Phase 2 trials published in this issue of *OA&C* (REF: Watt, Krupka) investigated the efficacy of 2 different small molecule selective TrkA inhibitors for knee OA pain. ASP7962 was administered orally (REF: Watt), and GZ389988A by intra-articular injection(REF: Krupka), each tested for the primary endpoint of pain reduction at 4 weeks. The trial of ASP7962 did not achieve this primary endpoint (in

[*]Corresponding author Address: Academic Rheumatology, University of Nottingham Clinical Sciences Building, Nottingham City Hospital, Hucknall Road, Nottingham, NG5 1PB, UK, Tel: 0115 823 1766, Fax: 0115 823 1757, david.walsh@nottingham.ac.uk.

Competing Interests: The views expressed in this editorial represent the views of the authors and entities named as competing interests have had no involvement in its preparation.

DAW: Consulting for AbbVie Inc., Eli Lilly and Company Ltd, GlaxoSmithKline Plc, Pfizer Ltd.

TN: Consulting for Pfizer Ltd., Regeneron

contrast to a third group who received naproxen 500mg bid), whereas that of GZ389988A indicated analgesic efficacy, albeit with a small clinical effect (a mean difference of change from baseline between the groups of <10 points out of a 0–100 scale). Secondary outcomes of some analgesic response rates (approximately 10% above placebo treatment), and a lack of reductions in use of rescue medications with active treatment were similar between the trials. Why might the two trials evaluating TrkA inhibition come to differing conclusions, or differ from trials of NGF-blocking antibodies?

Study population differences between the trials might have contributed to better signal detection over placebo in the trial of GZ389988A. Both studies recruited participants with moderate-to-severe knee pain plus radiographic OA, with broadly similar demographics, although participants in the trial of GZ389988A had slightly higher baseline pain. The GZ389988A trial specifically excluded participants with high scores on painDETECT, a classification tool for neuropathic-like pain for which high scores have been associated with central sensitization in people with knee OA.[3] Furthermore, the GZ389988A trial included only participants with minimal pain in the contralateral knee. Other pain below the waist has also been associated with evidence of central pain augmentation in OA knee pain.[4] Central pain augmentation predicts poor knee pain outcome from peripherally directed treatments such as arthroplasty.[5]

Pharmacological differences between GZ389988A and ASP7962 might lead to different trial outcomes. Neither study directly confirmed target engagement in the study participants, and it is possible that the lower affinity of ASP7962 for TrkA, or the lipophilic nature of GZ389988A affected the extent of TrkA blockade. The source of OA pain remains uncertain, but probably includes both synovium and subchondral bone, each of which contains peptidergic sensory nerves and cells that produce NGF.[6,7] Penetration of these discrete biological compartments might differ between pharmacological agents. A major question for the oral TrkA inhibitor formulation is whether, despite careful preclinical and Phase 1 studies, the investigators advanced the most effective dosing regimen for the Phase 2 trial. Both agents are selective, rather than specific for TrkA. Affinity of GZ389988A for colony stimulating factor 1 (CSF1R) receptors was similar to that for TrkA, such that analgesia following GZ389988A administration might not necessarily be solely attributable to TrkA inhibition.

Placebo analgesia was high in both trials, more than twice the treatment effect. Placebo effects were higher with intra-articular rather than oral treatment, consistent with previous systematic reviews.[8] Blinding to treatment arm is particularly important where placebo effects are substantial. Intra-articular GZ389988A injection was associated with pain, synovitis and raised CRP, with injection site inflammation in two thirds of participants. Injection site inflammation was not observed in any participant receiving placebo injection. Incomplete blinding and transient increases in pain might have increased subsequent analgesia in patients who received GZ389988A, and such analgesia might be independent on any specific inhibition of TrkA. Depression and anxiety scores were higher, contralateral OA more prevalent and baseline WOMAC pain scores lower in the placebo than in the GZ389988A arm, each of which might have led to an overestimation of apparent specific analgesic effect.

Clinical development of NGF-blocking antibodies has been hampered by the detection in Phase 3 studies of rare but important treatment emergent adverse events characterized as rapidly progressive OA (RPOA), particularly in those patients who also were using NSAIDs. It is unclear as to whether blockade of NGF binding to the TrkA or p75 receptor, or some as yet other unidentified mechanism contributes to the RPOA risk of anti-NGF therapies. In mice, the majority of sensory nerve fibers in bone express TrkA,[9] and chondrocytes and synoviocytes might also express TrkA.[7,10] NGF blockade or TrkA inhibition therefore each might disturb joint homeostasis. Even if TrkA inhibition avoided an increased risk of RPOA by merit of its lack of effect on p75 receptors, it is not yet clear whether there are any unintended adverse (or beneficial) consequences of additional inhibition of TrkB, TrkC, and, in the case of GZ389988A, also CSF1R, that might not be shared by NGF-blocking antibodies. Adverse events were higher in the active than placebo arms of both TrkA inhibitor trials reported here. Intra-articular GZ389988A injection was associated with injection site inflammation, and adverse events with ASP7962 were of similar frequency to with naproxen.

Rodent models have not convincingly replicated human RPOA associated with NGF blockade, so it is not possible to exclude this potential toxicity by preclinical testing of TrkA inhibitors. Some histological studies of pre-clinical OA models exposed to NGF-blocking antibodies have not demonstrated adverse effects on joint pathology, whereas others have detected possible increased chondropathy, synovitis, subchondral bone changes, or decreased TRAP-positive osteoclasts.[11] None of these changes, however, provides a close parallel to RPOA in humans. Furthermore, phase 2 trials of NGF blocking antibodies or TrkA inhibitors are not sufficiently powered to detect a small but important increase in risk of RPOA. RPOA was not detected in either TrkA inhibitor study reported here, although one subject in the GZ389988A group was found to develop a stress fracture at the medial tibial plateau of the injected knee. However, even if TrkA inhibition were found to be associated with RPOA, intra-articular administration might have lower risk simply by limiting exposure to the injected joint.

Given the lack of effective therapies available for many people with OA, new therapeutic agents are urgently needed to reduce the substantial public health burden of this disease that is now estimated to affect 300 million worldwide. The NGF-TrkA system is a promising therapeutic target that merits further development, particularly for patients in whom NSAIDs or opioids are contraindicated, not tolerated, or do not provide adequate pain relief. It is apparent from recent Phase 3 trials that the implemented risk mitigation strategies do not eliminate the risk of RPOA.[12–14] Greater biologic insight is needed into the mechanisms by which a small percentage of exposed patients might develop clinically important adverse joint events, in order to further optimize evidence-supported risk mitigation strategies for these agents.

Role of the funding source:

DAW is supported by Versus Arthritis 20777 and the UK National Institute for Health Research; the funding bodies had no involvement in this manuscript.

TN is supported by NIH K24 AR070892 and R01 AR062506; the funding body had no involvement in this manuscript.

References

1. Mantyh PW, Koltzenburg M, Mendell LM, Tive L, Shelton DL. Antagonism of nerve growth factor-TrkA signaling and the relief of pain. Anesthesiology 2011;115:189–204. [PubMed: 21602663]
2. Gowler PR, Walsh DA, Chapman V. Peripheral brain derived neurotrophic factor contributes to chronic joint pain in two animal models of osteoarthritis. Osteoarthritis Cartilage 2018;26:S15.
3. Hochman JR, Davis AM, Elkayam J, Gagliese L, Hawker GA. Neuropathic pain symptoms on the modified painDETECT correlate with signs of central sensitization in knee osteoarthritis. Osteoarthritis Cartilage 2013;21:1236–42. [PubMed: 23973136]
4. Akin-Akinyosoye K, Frowd N, Marshall L, Stocks J, Fernandes GS, Valdes A, et al. Traits associated with central pain augmentation in the Knee Pain In the Community (KPIC) cohort. Pain 2018;159:1035–44. [PubMed: 29438225]
5. Wylde V, Beswick A, Bruce J, Blom A, Howells N, Gooberman-Hill R. Chronic pain after total knee arthroplasty. EFORT Open Rev 2018;3:461–70. [PubMed: 30237904]
6. Walsh DA, McWilliams DF, Turley MJ, Dixon MR, Franses RE, Mapp PI, et al. Angiogenesis and nerve growth factor at the osteochondral junction in rheumatoid arthritis and osteoarthritis. Rheumatology (Oxford) 2010;49:1852–61. [PubMed: 20581375]
7. Manni L, Lundeberg T, Fiorito S, Bonini S, Vigneti E, Aloe L. Nerve growth factor release by human synovial fibroblasts prior to and following exposure to tumor necrosis factor-alpha, interleukin-1 beta and cholecystokinin-8: the possible role of NGF in the inflammatory response. Clin Exp Rheumatol 2003;21:617–24. [PubMed: 14611111]
8. Bannuru RR, McAlindon TE, Sullivan MC, Wong JB, Kent DM, Schmid CH. Effectiveness and Implications of Alternative Placebo Treatments: A Systematic Review and Network Meta-analysis of Osteoarthritis Trials. Ann Intern Med 2015;163:365–72. [PubMed: 26215539]
9. Castaneda-Corral G, Jimenez-Andrade JM, Bloom AP, Taylor RN, Mantyh WG, Kaczmarska MJ, et al. The majority of myelinated and unmyelinated sensory nerve fibers that innervate bone express the tropomyosin receptor kinase A. Neuroscience 2011;178:196–207. [PubMed: 21277945]
10. Gigante A, Bevilacqua C, Pagnotta A, Manzotti S, Toesca A, Greco F. Expression of NGF, Trka and p75 in human cartilage. Eur J Histochem 2003;47:339–44. [PubMed: 14706929]
11. Miller RE, Block JA, Malfait AM. Nerve growth factor blockade for the management of osteoarthritis pain: what can we learn from clinical trials and preclinical models? Curr Opin Rheumatol 2017;29:110–8. [PubMed: 27672741]
12. Schnitzer TJ, Easton R, Pang S, Levinson DJ, Pixton G, Viktrup L, et al. Effect of Tanezumab on Joint Pain, Physical Function, and Patient Global Assessment of Osteoarthritis Among Patients With Osteoarthritis of the Hip or Knee: A Randomized Clinical Trial. JAMA 2019;322:37–48. [PubMed: 31265100]
13. Pfizer and Lilly announce top-line results from long-term phase 3 study of tanezumab in patients with osteoarthritis [press release]. New York, NY: Pfizer; 4 18, 2019 (Accessed July 1, 2019, at https://www.pfizer.com/news/press-release/press-release-detail/pfizer_and_lilly_announce_top_line_results_from_long_term_phase_3_study_of_tanezumab_in_patients_with_osteoarthritis.)
14. Regeneron and Teva Announce Positive Topline Phase 3 Fasinumab Results in Patients with Chronic Pain from Osteoarthritis of the Knee or Hip. [press release] Tarrytown, NY: Regeneron; 8 16, 2018 (Accessed July 1, 2019, at https://investor.regeneron.com/index.php/news-releases/news-release-details/regeneron-and-teva-announce-positive-topline-phase-3-fasinumab.)