

# Osteoarthritis and Cartilage



## Editorial

### A tale of two TrkA inhibitor trials: same target, divergent results



**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<sup>1</sup>. 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.<sup>2</sup>

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 contrast to a third group who received naproxen 500 mg 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<sup>3</sup>. 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<sup>4</sup>. Central pain augmentation predicts poor knee pain outcome from peripherally directed treatments such as arthroplasty.<sup>5</sup>

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<sup>6,7</sup>. 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<sup>8</sup>. 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<sup>9</sup>, and chondrocytes and synoviocytes might also express TrkA<sup>7,10</sup>. 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<sup>11</sup>. 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<sup>12–14</sup>. 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.

## Author contributions

Both authors contributed equally to this work.

## 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.

## 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.

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D.A. Walsh\*  
*Pain Centre Versus Arthritis, and NIHR Nottingham Biomedical Research Centre, Academic Rheumatology, University of Nottingham, UK*

T. Neogi  
*Section of Rheumatology, Boston University School of Medicine, USA*  
*E-mail address:* [tneogi@bu.edu](mailto:tneogi@bu.edu).

\* Address correspondence and reprint requests to: D.A. Walsh, Academic Rheumatology, University of Nottingham, Clinical Sciences Building, Nottingham City Hospital, Hucknall Road, Nottingham, NG5 1PB, UK. Tel: 115-823-1766; Fax: 115-823-1757.  
*E-mail address:* [david.walsh@nottingham.ac.uk](mailto:david.walsh@nottingham.ac.uk) (D.A. Walsh).