

Inhibition of the JAK/STAT pathway and granulocyte macrophage colony stimulating factor: emerging therapeutic approaches in pain modulation in patients with rheumatoid arthritis

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Article Type: Correspondence – reply

Total: 400/400 words

References: 5/5

Keywords: central sensitisation, JAK-STAT, JAK inhibitor, GM-CSF, pain, rheumatoid arthritis, cytokines

We read with interest the review by Nijs and colleagues¹ describing central sensitisation in chronic pain conditions and latest discoveries. We agree with the authors that pain represents a significant unmet need. Here we describe the emerging nociceptive therapeutic potential of immunomodulatory strategies.

The aetiology of primary chronic pain syndromes (e.g. fibromyalgia) is poorly understood and the significance of peripheral blood cytokine signatures remains unclear². Many patients with rheumatoid arthritis (RA) continue to experience pain, despite adequate control of inflammation. Pathomechanisms underlying this 'residual pain' in RA may be attributable to a complex interaction of subclinical synovitis, structural damage and peripheral and central sensitisation. The development of widespread pain and central sensitisation in RA may be due to sustained inflammatory input on peripheral nerves, as well as a decreased threshold (allodynia) and increased responsiveness (hyperalgesia) to noxious stimuli. It is unclear when central sensitisation patterns are established in the disease course of RA, if they are reversible or amenable to targeted therapies.

The Janus kinase/signal transducer and activator of the transcription (JAK-STAT) is a complex intracellular cascade involving both pro- and anti-inflammatory cytokines. The precise role of the JAK-STAT pathway in nociception is yet to be fully elucidated, but several cytokine receptors associated with pain are expressed on afferent nerves. There is accumulating evidence to suggest that targeting the JAK-STAT pathway may improve pain outcomes in RA³. A recent post-hoc analysis of the RA-BEAM phase III clinical trial, found that patients with RA treated with baricitinib (JAK1/2 inhibitor) achieved greater and more rapid improvements in patient-reported pain than patients treated with adalimumab (tumour necrosis factor α inhibitor), despite similar improvements in swollen joint counts⁴. These findings suggest that JAK inhibition may modulate both inflammatory and non-inflammatory pain pathways, and that simultaneous suppression of multiple cytokines that amplify pain may be more effective than selective cytokine blockade³.

Granulocyte macrophage colony stimulating factor (GM-CSF) is a pro-inflammatory cytokine, signalling through JAK2 homodimers, implicated in the pathogenesis of RA, as well as pain modulation pathways, thought mainly to be driven via the chemokine CCL17 axis. Data from experimental arthritis models suggest that GM-CSF may contribute to mechanical hyperalgesia in RA. Recent results from clinical trials targeting GM-CSF in patients with RA show significant analgesic efficacy, supporting its role as a nociceptive cytokine⁵.

Further research is warranted to better understand whether these findings from rheumatoid arthritis can be extrapolated to chronic pain syndromes.

Author Contribution:

PM and PCT drafted the manuscript. All authors contributed to discussions, revised and approved the manuscript.

Disclosures

PM is an MRC-GSK EMINENT clinical training fellow with project funding outside the submitted work. PM has served on an advisory board for SOBI. PM receives co-funding by the NIHR University College London Hospitals Biomedical Research Centre (UCLH BRC). PM reports consultancy fees from Lily and SOBI, outside the submitted work. CC receives funding from Versus Arthritis, UCLH BRC, Action Medical, Lupus UK outside the submitted work. CC has received consultancy fees from Roche and ModernBiosciences, and educational financial support from Novartis, Lilly, Chugai outside the submitted work. PCT has received research grants from Celgene, Galapagos and Lilly and consultancy fees from GSK, AbbVie, Lilly, Pfizer, Gilead and Galapagos outside the submitted work. AR reports consultancy fees from Lilly and Chugai outside the submitted work.

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