Review

JAK/STAT pathway and nociceptive cytokine signalling in rheumatoid arthritis and psoriatic arthritis

N. Crispino[1], F. Ciccia[2]

[1]Medical Department, Pfizer Italy, Rome; [2]Department of Precision Medicine, Rheumatology Section, University of Campania Luigi Vanvitelli, Naples, Italy.

Natascia Crispino, MD, PhD
Francesco Ciccia, MD, PhD

Please address correspondence to:
Francesco Ciccia,
Dipartimento di Medicina di Precisione, Sezione di Reumatologia, Università degli Studi della Campania Luigi Vanvitelli,
Via Sergio Pansini 5,
80100 Napoli, Italy.
E-mail: francesco.ciccia@unicampania.it

Received on March 11, 2020; accepted in revised form on August 31, 2020.

Clin Exp Rheumatol 2021; 39: 668-675.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2021.

Key words: JAK/STAT, nociception, cytokine signalling, rheumatoid arthritis, psoriatic arthritis, tofacitinib

Competing interests: F. Ciccia received an honorarium from Pfizer in connection with the development of this manuscript. N. Crispino is a Pfizer employee.

ABSTRACT

The key role of pro-inflammatory cytokines in the pathogenesis of rheumatoid arthritis (RA) and psoriatic arthritis (PsA) is strongly supported by the observation that their blockage is effective in the treatment of these diseases. Indeed, blockade of cytokine signal transduction mechanisms, including the JAK-STAT pathway, may be critical in the treatment of RA and PsA. The Janus kinase (JAK) inhibitors tofacitinib and baricitinib target JAKs with high potency and have a well-established rationale for clinical therapeutic use in RA and PsA by affecting multiple cytokines involved in both development and propagation of the disease. Nociceptive responses are also important to consider in the treatment RA and PsA. In this regard, cytokines have also been implicated in modulation of pain and nociception and the JAK/STAT pathway is receiving increasing attention in modulation of nociceptive responses given to its clear role in cytokine signalling. Therefore, inhibition of JAK/STAT pathway with specific JAK inhibitors has the potential to modulate pain in patients with RA and PsA. Data from randomised controlled trials and real-world settings on large numbers of patients with RA (tofacitinib and baricitinib) and randomised controlled trials in patients with PsA (tofacitinib) have shown that a rapid effect on the pain component in these diseases is observed. Thus, it can be hypothesised that JAK inhibitors may have a dual therapeutic role by modulating inflammation and nociception, which leads to clinical benefits including reduction of pain beyond that related to inflammation. The present review will overview the impact of pain in patients with rheumatic disease and the physiological basis of modulating nociceptive pain. Current knowledge about the role of cytokines in mediation of pain and the involvement of the JAK/STAT pathway in modulating nociceptive responses will then be summarised, followed by an analysis of clinical data on pain modulation by JAK inhibitors in the treatment of RA and PsA.

Introduction

Psoriatic arthritis (PsA) and rheumatoid arthritis (RA) are chronic, inflammatory diseases of the joints and sites where tendons and ligaments connect to bone (1, 2). Although the aetiology of both diseases is still elusive, it is clear that the aberrant activation of the immune system, through hyperexpression of pro-inflammatory cytokines, plays a fundamental role in inducing swelling, pain, and stiffness in joints. Cytokines are small secreted proteins (~5–20 kDa) released by cells that have a specific effect on the interactions and communications between cells (3). The role of pro-inflammatory cytokines such as IL-6, IL-1, IL-23/IL-17, and TNF-α in the pathogenesis of RA and PsA is strongly supported by the evidence that their blockage is effective in the treatment of these diseases (4, 5). More recently, it has been shown that blockade of cytokine signal transduction mechanisms, many of which are mediated by the Janus kinase-signal transducers and activators of transcription (JAK-STAT) pathway, may also be critical in the treatment of RA and PsA (6). JAK inhibitors (Jakinibs) target multiple JAKs with high affinity and have a well-established rationale for clinical therapeutic use in inflammatory and autoimmune diseases by blocking multiple cytokines involved in both development and propagation of the disease (7).

Tofacitinib and baricitinib are oral, reversible inhibitors of JAK3, JAK1

(tofacitinib) and JAK1 and JAK2 (baricitinib) with immunomodulatory and anti-inflammatory activities (8). Upon administration, tofacitinib and baricitinib bind to JAK to prevent the activation of the JAK-STAT signalling pathway. This, in turn, decreases the production of pro-inflammatory type I and II cytokines, such as interleukin (IL)-6, IL-7, IL-15, IL-21, IFN-α and IFN-β, thus diminishing both an inflammatory response and inflammation-induced damage caused by dysregulated activation of immune system (9). Data from clinical studies indicate a powerful effect on modulation of pain in patients with RA and PsA (tofacitinib) and RA (baricitinib). This raises the question of whether the effects of JAK-inhibitors on the pain component is linked to an indirect effect, due to the shutdown of joint inflammation, or if it is an effect intrinsically related to the inhibition of the JAK/STAT pathway. The latter hypothesis does not seem remote given the function of JAKs and other major regulators of gene expression such as cytokines in mediating nociception. The present review will firstly overview the impact of pain in patients with rheumatic diseases and the physiological basis of nociceptive pain modulation. Current knowledge on the role of type I and type II cytokines on mediating pain and the involvement of the JAK/STAT pathway in modulating nociceptive responses will then be summarised, followed by an analysis of the clinical data for tofacitinib in the treatment of RA and PsA.

Burden of pain in rheumatic diseases

Pain is the most common symptom for consulting a rheumatologist and can no longer be viewed as an isolated symptom (10, 11). The consequences of chronic pain, with its negative effects on sleep, mood and energy, cause global suffering of the individual patient; as such, reduction of pain should be a primary goal of clinical management of rheumatic diseases (12). Pain also seems to be an influential factor of overall health status, and improving pain during treatment of rheumatic diseases may help to reduce socioeconomic inequalities in general health status (13). It is recommended that pain should be adequately assessed using dedicated questionnaires in addition to narrative descriptions (12). A recent study has shown that patients with diverse rheumatic diseases share similar patient-reported outcome measures and significant patterns of healthcare resource utilisation, with substantial costs of comorbidities (14). As a major burden to society, novel approaches for the treatment of pain are thus needed to improve care of patients with rheumatic diseases (14-16).

The physiological basis of pain modulation

Nociception is the process by which thermal, mechanical, or chemical stimuli are detected as pain by a specific type of peripheral nerve fibre, called nociceptors (17). The dorsal root ganglia (DRG) contain the cell bodies of nociceptors and have a peripheral axonal branch that innervates their target organ as well as a central branch that innervates the spinal cord. The activation of the nociceptors takes place only when the intensity of the applied stimulus reaches the range of danger and damage (17). This selectivity suggests that nociceptors have biophysical and molecular properties that allow them to respond exclusively to potentially harmful stimuli.

Various evidence indicates that different pro-inflammatory cytokines can act directly or indirectly on nociceptive neurons. For example, the endings of nociceptive sensory neurons express pro-inflammatory cytokine receptors, and the application of cytokines in vitro to cultured isolated sensory neurons activates second messenger systems, modifies excitability and ionic currents, and regulates molecules involved in nociception. In addition, the injection of some pro-inflammatory cytokines into healthy tissues evokes painful behaviours in animals and improves the speed of response of nociceptive sensory fibres. Furthermore, neutralisation of pro-inflammatory cytokines can reduce pain even before the reduction of the inflammatory process has occurred (18-22). Therefore, cytokines can contribute to pain both indirectly, by inducing the release of other mediators that act on neurons (*e.g.* prostaglandins), and directly, on the neurons themselves.

Role of cytokines in the modulation of pain

Several studies, mostly in animal models, have indicated that type I and II cytokines such as IL-6, IL-1β and IL-23 may play a central role in mediation of pain. IL-1β is an important mediator of cell recruitment and activation, potentially driving local tissue damage evident, for example, in an inflamed arthritic joint. The role of IL-1β in modulating nociception is supported by the evidence that the IL-1 receptor (IL-1R) is expressed by rat DRG neurons and increased during complete Freund's adjuvant (CFA)-induced arthritis (23-25). In the rat adjuvant induced arthritis (AIA) model, the administration of the IL-1R antagonist anakinra resulted in inhibition of thermal hypersensitivity, mainly by inducing the down-regulation of TRPV1 (transient receptor potential cation channel subfamily V member 1) in DRG neurons, which is involved in thermal hypersensitivity (26). IL-1β also increases the mechanosensitivity of C fibres, but reduces that of Aδ fibres in the rat knee joint. IL-6 is a key cytokine involved in the pathogenesis of RA (27). An early study in IL-6 deficient mice indicated that nociceptive responses were aberrant in the peripheral nerve section, strongly suggesting that IL-6 is involved in nociception and raising the possibility that IL-6 might be a target in the study and modulation of pain (28, 29). The fundamental role of IL-6 signalling in modulating nociception is also supported by the evidence that DRG neurons and glial cells of the spinal cord express IL-6R and gp130, and knock-out mice lacking gp130 in sensory DRG neurons (SNS-gp130$^{-/-}$) have reduced inflammatory and tumour-induced pain (30-32). In addition, IL-6 is likely to be involved in a number of different types of pain modulation as demonstrated by a recent study examining cold stress in a rat model of neuropathic pain wherein the alpha 2-adrenoceptor agonist dexmedetomidine appeared to act by inhibiting IL-6 and TNF-α (33). IL-6 may also work in

coordination with other cytokines such as IL-23, IL-17A, and IL-18, as well as their receptors, given the increased expression of all these molecules in a rat model of sciatic stimulation (34).

The IL-23/IL-17 axis also seems to be a fundamental pathway involved in nociception. In addition to Th17 cells, IL-17 is also produced by other T cell subsets and innate immune cells expressing the IL-23 receptor and all become pathogenic after exposure to IL-23 (35). For signalling, IL-23 triggers heterodimerisation of IL-12Rβ1 and the IL-23 receptor and subsequent activation of downstream signal transduction pathways including JAK/STAT (mainly STAT3), MAP kinase, and PI3K (35). Conversely, IL-17A signalling requires the formation of a heterotrimeric receptor complex comprising IL-17RA and IL-17RC that are single pass type I membrane receptors containing an intracellular signalling motif referred to as the SEFIR domain. A SEFIR domain is also present in Act1, an adaptor protein with E3 ligase activity that orchestrates homotypic interactions with the SEFIR motif of the IL-17 receptors, mainly leading to TRAF6-dependent activation of the NF-κB and MAP kinase pathways (36-41).

Although IL-23 has not been directly involved in the modulation of nociception, several investigations have suggested that IL-17, directly modulated by IL-23, is implicated in the mechanisms of pain. In this regard, in DRG sections and in cultured DRG neurons, the majority of neurons show cytoplasmatic expression of IL-17RA (42, 43). IL-17 has been demonstrated to be a pro-nociceptive cytokine in the boswellic acid (BSA)-induced model of arthritis. In this model, the pro-nociceptive IL-17A effect depends on both neutrophil migration and various pro-inflammatory mediators, such as TNF-α, IL-1β, CXCR1/2 chemokine ligands, MMPs, endothelins, prostaglandins, and sympathetic amines (44). IL-17 also contributes to neuroinflammatory responses and pain hypersensitivity following neuropathic injury as demonstrated by the finding that, compared to wild-type, IL-17 knockout mice display significantly decreased mechanical pain hypersensitivity as well as decreased infiltration of T cells and macrophages to injured sciatic nerves and L3-L5 dorsal root ganglia. These mice showed a decreased activation of microglia and astrocytes in the L3-5 dorsal and ventral horns of the spinal cord (45). In mice with unilateral AIA in the knee, an antibody against IL-17 improved the guarding score and reduced secondary mechanical hyperalgesia at the ipsilateral paw. The severity and time course of AIA, however, have been demonstrated to be indistinguishable in wild-type and IL-17A knockout mice even though these litter mice show less mechanical hyperalgesia than wild-type mice; this indicates that IL-17A contributes to pain, even if it is not crucial for arthritis (46). In addition, astrocytes seem to be the major cellular source of spinal IL-17A and astrocytic IL-17A plays an important role in the maintenance of neuropathic pain through the CaMKII/CREB signalling pathway in the spinal cord. Together, all these findings raise the possibility that a complex type I and II cytokine network may be involved in pain modulation (34, 47, 48).

Table I. Cytokines involved in the pathogenesis of RA and PsA in the modulation of pain and role of tofacitinib in directly or indirectly modulating their expression.

Cytokine	RA	PsA	Effect on Pain	Direct Tofa effect	Indirect Tofa effect
IFN-α/β	+	-	-	+	-
IFN-γ	-	+	-	+	-
IL-1	+	+	+	-	+
IL-2	-	+	-	+	-
IL-6	+	+	+	+	-
IL-7	+	+	-	+	-
IL-10	+	+	-	+	-
IL-12	+	+	-	+	-
IL-15	+	+	-	+	-
IL-17	+	+	+	-	+
IL-18	+	+	-	-	-
IL-21	+	-	-	+	-
IL-22	-	+	-	+	-
IL-23	+	+	±	+	-
GM-CSF	+	-	-	-	+
TGF-β	+	-	-	-	-
TNF-α	+	+	-	-	-

Role of the JAK/STAT pathway in modulating nociception

The JAK/STAT pathway is a pleiotropic pathway used to transduce a multitude of signals for development and homeostasis in animals, from humans to flies (49). The JAK-STAT pathway is also implicated in the pathogenesis of various inflammatory and autoimmune diseases, including RA, PsA, and chronic inflammatory bowel diseases (49), since many of the cytokines involved use JAK and STAT to transduce intracellular signals. The success of small molecule Jakinibs in the treatment of various rheumatological diseases shows that intracellular signalling pathways can be therapeutically targeted to treat chronic inflammatory diseases. Beyond the powerful anti-inflammatory effect mediated by Jakinibs, clinical use in real-life settings demonstrates a dramatic effect on the pain component of RA and PsA patients (50, 51). This effect appears to be attributable to the action of these drugs in reducing the concentration of type I and II cytokines involved in the induction of inflammation and pain in these diseases. Several lines of evidence, however, suggest that the JAK/STAT pathway may be directly involved in the mechanisms that regulate nociception. Alterations in the JAK/STAT pathway have been directly implicated in pain modulation in a number of animal studies on pain. JAK/STAT3 signalling also plays a major role in spinal cord plasticity and mechanical allodynia associated with peripheral nerve injury. Spinal nerve lesion leads, in fact, to rapid activation of the JAK/STAT3 pathway in dorsal spinal cord microglia in relation with enhanced levels of spinal IL-6. Inactivation of JAK/STAT3

signalling in rat dorsal spinal cord glia through local, lentiviral-mediated production of the suppressor of cytokine signalling SOCS3, a physiologic inhibitory protein of JAK/STAT3, prevented the abnormal expression of IL-6, CC chemokine ligand CCL2, and activating transcription factor ATF3 induced in the spinal cord by chronic constriction injury of the sciatic nerve and substantially attenuated mechanical allodynia in rats (52). Emerging lines of evidence indicate that peripheral nerve injury converts resting spinal cord glia into reactive cells that are required for the development and maintenance of neuropathic pain. Tsuda *et al*. recently demonstrated that nerve injury-induced astrocyte proliferation requires the JAK/STAT3 signalling pathway (53). Nerve injury induces, in fact, marked STAT3 nuclear translocation in dorsal horn astrocytes. Intrathecally administration of inhibitors of JAK signal transducers and ATF3 signalling to rats with nerve injury reduced the number of proliferating dorsal horn astrocytes and produced a recovery from established tactile allodynia, a cardinal symptom of neuropathic pain that is characterised by pain hypersensitivity evoked by innocuous stimuli (53). JAK/STAT3 alterations have also been shown in diverse models of pain such as that induced by electroacupuncture and by oxaliplatin, both of which show common increases in activation of STAT3 (54, 55). JAK/STAT3 involvement is also found in models of pain in collagen-induced arthritis in mice, as the anti-inflammatory agent baicalin improves pain and concomitantly suppresses JAK1/STAT3 signalling (56). In addition, the RAGE/STAT3 pathway has been reported to be activated during central spinal central sensitisation and persistent lumbar disc pain related to herniation (57, 58). A complexity of molecules has been implicated in JAK/STAT signalling as mediator of neuropathic pain, including IL-33 and its receptor ST2 (59) as well as CAV-1-NR2B (60), miR-98 (61), leptin (62), Nav1.6 (63), NLRP3 (64), and PKM2 (65). These findings support the fundamental role of JAK/STAT pathway in directly modulating different nociceptive pathways.

Table II. Patient-reported assessment of pain with tofacitinib in rheumatoid arthritis.

Reference	Duration	VAS* pain changes from baseline in units (%)			
		Tofacitinib		Placebo	Comparator DMARD
		5 mg BID	10 mg BID		
Strand *et al*. (71)	3 months	-26.74	-27.82	-9.50	Adalimumab -22.49
Strand *et al*. (72)	3 months	-27.16	-24.95	-8.26	-
Strand *et al*. (69)	24 months	-34.79	-37.62	-	Methotrexate -29.67
Strand *et al*. (51)	3 months	-24.2	-26.8	-11.4	-
Strand *et al*. (70)	24 months	-20.5	-21.3	-	-
Strand *et al*. (73)	6 months	-29.19	-34.11	-	-

*VAS: visual analogue scale for pain is a unidimensional measure of pain intensity consisting in a straight line with the endpoints defining extreme limits of pain perception such as 'no pain' and "worse pain"

Tofacitinib and baricitinib in the modulation of pain: data from randomised clinical trials in rheumatoid arthritis and psoriatic arthritis

Tofacitinib is a selective JAK inhibitor that preferentially inhibits JAK1 and JAK3. Tofacitinib, directly or indirectly, modulates many of the pro-inflammatory cytokines involved in modulation of pain (Table I). Several clinical studies of ≤24 months duration showed that tofacitinib monotherapy (as first or second-line treatment) and combination therapy with a conventional synthetic DMARD (csDMARD; as second or third-line treatment) was effective in reducing signs and symptoms of disease and improving health-related quality of life (66, 67). Based on these results, tofacitinib was approved by the FDA and EMA for the treatment of moderate to severe RA and PsA.

Baricitinib is a small molecule that selectively inhibits JAK1 and JAK2, and is approved for use as monotherapy, or in combination with methotrexate, for the treatment of adult patients with moderate to severe active RA whith inadequate response or intolerance to ≥1 DMARD (68).

Given the extensive clinical trials with tofacitinib in RA and PsA and baricitinib in RA, it is worthwhile to overview the effects that these JAK inhibitors have on pain in these inflammatory conditions.

Tofacitinib in RA

The efficacy of tofacitinib in improving patient reported outcomes (PRO), including pain, has been demonstrated in several placebo-controlled, double-blind phase III RCT studies, all of which assessed the impact of tofacitinib on pain in patients with RA: ORAL Start (69), ORAL Scan (70), ORAL Sync (51), ORAL Standard (71), ORAL Step (72), and ORAL SOLO (73) (Table II). These studies lasted 6–24 months and patients were randomised to receive tofacitinib 5 mg twice daily (BID), tofacitinib 10 mg BID, or placebo except in the ORAL Standard study, where patients were also randomised to an active control arm of adalimumab 40 mg once every 2 weeks. In the ORAL Step study, evaluating patients with RA and inadequate response to csDMARD, significant improvements in pain score were evident as early as week 2 and were observed at months 3 and 6 with tofacitinib 5 mg and 10 mg BID compared to placebo. At month 3, changes in least square mean (LSM) from baseline outweighed the differences clinically important minimum (MCID) in pain (>10 points) for both doses of tofacitinib (72).

In the 24-month randomised controlled phase III ORAL Start study, patients with moderately to severely active RA who were naive for MTX, reported statistically significant improvements in pain with tofacitinib 5 and 10 mg monotherapy, which was maintained for 24 months (69).

In the 12-month randomised controlled phase III trial (ORAL Sync), patients with active RA and previous inadequate response to ≤1 conventional or biological DMARD therapy were randomised to tofacitinib 5 mg BID, tofacitinib 10 mg BID, placebo, in combination with

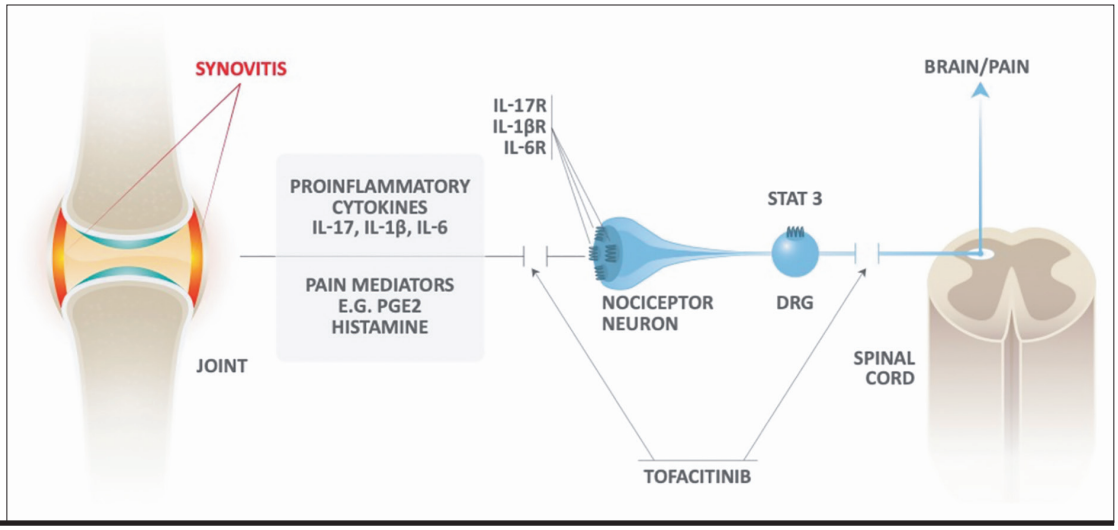

Fig. 1. Schema showing the hypothesised role of tofacitinib in modulating inflammation and nociception.

stable background DMARD therapy. At month 3, treatment with tofacitinib 5 mg twice daily and 10 mg BID led to significantly greater improvements from baseline in patient assessment of pain score than placebo. These changes from baseline were sustained through month 12 (51).

The randomised controlled phase 3 ORAL Scan study evaluated the impact of 24 months tofacitinib treatment on PROs in patients with active RA and inadequate responses to methotrexate (MTX-IR). Patients who received tofacitinib reported significant reductions in pain compared to placebo at month 3, sustained through month 24, similarly to placebo-treated patients after advancement (70).

In the ORAL Solo study 6-month randomised, placebo-controlled, phase III trial in patients with inadequate response to disease-modifying antirheumatic drugs (DMARD-IR), tofacitinib 5 mg and 10 mg BID was evaluated *versus* placebo monotherapy. The results showed improvement in pain from baseline as early as 3 days after starting tofacitinib treatment. Statistically significant changes from baseline and further improvements occurred until month 6 in both active treatment groups (73). All these studies support the efficacy of tofacitinib in reducing pain in RA patients (Fig. 1).

Tofacitinib in PsA

The impact of tofacitinib on pain as a PRO in PsA in patients with PSA and an inadequate response to TNF inhibitors and in those with inadequate response to conventional DMARDs has been extensively studied (50, 74). In both patient populations, tofacitinib was associated with clinically-meaningful benefits on pain. Improvements were relatively rapid, significant vs placebo and sustained throughout the treatment period of 6 or 12 months. These improvements were reflected in patients advancing from placebo to tofacitinib 5 or 10 mg BID, who reported similar improvements after month 3.

More recently, mediation modelling was used to examine data from the Phase 3 OPAL Broaden and Beyond trials (75). Mediation modelling attempts to understand the mechanisms behind an observed relationship and independent and dependent variables using other explanatory variables (*i.e.* mediators). In this model, pain was the designated dependent variable, tofacitinib 5 mg BID *versus* placebo the independent variable, and inflammation [measured by swollen joint count (SJC) and C-reactive protein (CRP)] was the mediator. It was found that 25.9% of the treatment effect of tofacitinib on pain was mediated by CRP/SJC (indirect effect), of which changes via CRP and SJC were 17.8% and 8.1%, respectively. The treatment effect on pain not attributable to CRP/SJC (direct effect) was 74.1%. This appears to suggest that CRP/SJC-associated inflammation might only partially account for the observed improvement in pain in PsA, and that other potential mediators may be responsible for part of the observed effect of tofacitinib on pain. The effects of tofacitinib on residual pain in PsA has also been investigated using data from OPAL Broaden trial (76). This analysis examined patients with 'residual pain' at month 3, which was considered as pain in patients with complete attenuation of inflammation, SJC of 0, and CRP levels <6 mg/L. At month 3, 23.5% of patients had achieved SJC of 0 and CRP <6 mg/L; more tofacitinib-treated (tofacitinib 5 mg BID; tofacitinib 10 mg BID) and adalimumab-treated patients achieved SJC of 0 and CRP <6 mg/L *versus* placebo. When considering absolute (residual) pain at month 3, mean residual pain was similar across treatment groups, despite higher baseline pain in the tofacitinib groups. Changes from baseline in pain and absolute pain at month 3 suggested that in patients with PsA whose inflammation was completely attenuated, tofacitinib might have an effect on residual pain that was not obviously attributable to inflammation. This analysis would appear to indirectly confirm the results with mediation modelling, although additional studies will be needed to confirm these data. Taken together, in addition to objective improvements in clinical disease responses to tofacitinib in both RA and PsA, meaningful improvements have been reported in patient-reported pain in both diseases.

Baricitinib in RA

In the recent randomised, double-blind trial RA-BEAM (NCT0170358), the proportion of patients who achieve

pain relief thresholds, the time needed to reach the thresholds, and the relationship between pain and inflammation among patients with RA and an inadequate response to methotrexate was assessed (77). The trial compared baricitinib, adalimumab, and placebo plus methotrexate. Pain was evaluated by patient's assessment on a 0-100 mm visual analogue scale (VAS). Baricitinib-treated patients more likely achieved ≥30%, ≥50%, and ≥70% pain relief than placebo- and adalimumab-treated patients, as early as Week 1 *versus* placebo and at Week 4 *versus* adalimumab. Baricitinib-treated patients demonstrated consistent pain relief independently of levels of inflammation. A recent study compared improvement in pain and physical function in RA patients treated with baricitinib, adalimumab, tocilizumab and tofacitinib monotherapy derived from randomised, methotrexate (MTX)-controlled trials in csDMARDs/bDMARD naïve RA patients by using matching-adjusted indirect comparisons. Results from the study indicated greater pain reduction and improved physical function for baricitinib monotherapy when compared with tocilizumab and adalimumab. Interestingly, no statistically significant differences in pain reduction and improved physical function were observed between baricitinib and tofacitinib with the MAIC analyses (78). No data are currently available on the effect of baricitinib on pain in PsA patients.

Conclusions

Nociceptive responses are important aspects to consider in the treatment of rheumatic diseases such as RA and PsA. Cytokines have been implicated in the modulation of pain and nociception in these diseases and due to its clear involvement in cytokine signalling, the JAK/STAT pathway is receiving increasing attention in modulating nociceptive responses. Inhibition of the JAK/STAT pathway by specific Jakinibs has the potential to directly or indirectly mediate pain in patients with RA and PsA. Given the fundamental role of both type I and II cytokines in modulating nociception and the direct role of JAK/STAT pathway in modulating different nociceptive pathways, it seems reasonable to imagine that JAK/STAT inhibitors can play a fundamental role, direct or indirect, in the modulation of pain in patients with RA or PsA. Supporting this theoretical consideration are data from randomised controlled trials and real-world settings on large numbers of patients with RA (tofacitinib and baricitinib) and data from randomised controlled trials in patients with PsA (tofacitinib), which demonstrate a dramatic and rapid effect on the pain component of these patients, even before the resolution of the inflammatory process. Based on these data, it is possible to speculate that Jakinibs may have a dual therapeutic role: i) modulation of inflammation, producing the observed clinical benefits, and ii) modulation of nociception, which leads to a pain reduction beyond that related to inflammation. The impact of these drugs on other disease manifestations such as fatigue or on syndromes where pain is predominant, such as fibromyalgia, remains to be clarified.

Acknowledgement

Editorial and medical writing support was provided by HPS and was funded by Pfizer.

References

1. RIT CHLIN CT, COLBERT RA, GLADMAN DD: Psoriatic arthritis. *N Engl J Med* 2017; 376: 957-70.
2. MCINNES IB, SCHETT G: The pathogenesis of rheumatoid arthritis. *N Engl J Med* 2011; 365: 2205-19.
3. ALTAN-BONNET G, MUKHERJEE R: Cytokine-mediated communication: a quantitative appraisal of immune complexity. *Nat Rev Immunol* 2019; 19: 205-17.
4. ALUNNO A, CARUBBI F, GIACOMELLI R, GERLI R: Cytokines in the pathogenesis of rheumatoid arthritis: new players and therapeutic targets. *BMC Rheumatol* 2017; 1: 3.
5. TAN Y, QI Q, LU C *et al*.: Cytokine imbalance as a common mechanism in both psoriasis and rheumatoid arthritis. *Mediators Inflamm* 2017; 2017: 2405291.
6. A TV, HAIKARAINEN T, RAIVOLA J, SILVENNOINEN O: Selective JAKinibs: Prospects in Inflammatory and Autoimmune Diseases. *BioDrugs* 2019; 33: 15-32.
7. SCHWARTZ DM, BONELLI M, GADINA M, O'SHEA JJ: Type I/II cytokines, JAKs, and new strategies for treating autoimmune diseases. *Nat Rev Rheumatol* 2016; 12: 25-36.
8. PAIK J, DEEKS ED: Tofacitinib: a review in psoriatic arthritis. *Drugs* 2019; 79: 655-63.
9. GAO W, MCGARRY T, ORR C, MCCORMICK J, VEALE DJ, FEARON U: Tofacitinib regulates synovial inflammation in psoriatic arthritis, inhibiting STAT activation and induction of negative feedback inhibitors. *Ann Rheum Dis* 2016; 75: 311-5.
10. FITZCHARLES MA, LUSSIER D, SHIR Y: Management of chronic arthritis pain in the elderly. *Drugs Aging* 2010; 27: 471-90.
11. GOLDENBERG DL: The interface of pain and mood disturbances in the rheumatic diseases. *Semin Arthritis Rheum* 2010; 40: 15-31.
12. CHUA JR, CASTREJON I, PINCUS T: Assessment of pain and other patient symptoms in routine clinical care as quantitative, standardised, "scientific" data. *Clin Exp Rheumatol* 2017; 35 (Suppl. 107): S13-20.
13. VILEN L, BALDASSARI AR, CALLAHAN LF: Socioeconomic burden of pain in rheumatic disease. *Clin Exp Rheumatol* 2017; 35 (Suppl. 107): S26-31.
14. MARS NJ, KEROLA AM, KAUPPI MJ, PIRINEN M, ELONHEIMO O, SOKKA-ISLER T: Patients with rheumatic diseases share similar patterns of healthcare resource utilization. *Scand J Rheumatol* 2019; 48: 300-7.
15. AL MAINI M, ADELOWO F, AL SALEH J *et al*.: The global challenges and opportunities in the practice of rheumatology: white paper by the World Forum on Rheumatic and Musculoskeletal Diseases. *Clin Rheumatol* 2015; 34: 819-29.
16. MICHELSEN B, FIANE R, DIAMANTOPOULOS AP *et al*.: A comparison of disease burden in rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis. *PLoS One* 2015; 10: e0123582.
17. BASBAUM AI, BAUTISTA DM, SCHERRER G, JULIUS D: Cellular and molecular mechanisms of pain. *Cell* 2009; 139: 267-84.
18. CUNHA FQ, POOLE S, LORENZETTI BB, FERREIRA SH: The pivotal role of tumour necrosis factor alpha in the development of inflammatory hyperalgesia. *Br J Pharmacol* 1992; 107: 660-4.
19. HENSELLEK S, BRELL P, SCHAIBLE HG, BRAUER R, SEGOND VON BANCHET G: The cytokine TNFalpha increases the proportion of DRG neurones expressing the TRPV1 receptor via the TNFR1 receptor and ERK activation. *Mol Cell Neurosci* 2007; 36: 381-91.
20. INGLIS JJ, NOTLEY CA, ESSEX D *et al*.: Collagen-induced arthritis as a model of hyperalgesia: functional and cellular analysis of the analgesic actions of tumor necrosis factor blockade. *Arthritis Rheum* 2007; 56: 4015-23.
21. SOMMER C, KRESS M: Recent findings on how proinflammatory cytokines cause pain: peripheral mechanisms in inflammatory and neuropathic hyperalgesia. *Neurosci Lett* 2004; 361: 184-7.
22. WATKINS LR, WIERTELAK EP, GOEHLER LE, SMITH KP, MARTIN D, MAIER SF: Characterization of cytokine-induced hyperalgesia. *Brain Res* 1994; 654: 15-26.
23. COPRAY JC, MANTINGH I, BROUWER N *et al*.: Expression of interleukin-1 beta in rat dorsal root ganglia. *J Neuroimmunol* 2001; 118: 203-11.
24. LI M, SHI J, TANG JR *et al*.: Effects of complete Freund's adjuvant on immunohistochemical distribution of IL-1beta and IL-1R

I in neurons and glia cells of dorsal root ganglion. *Acta Pharmacol Sin* 2005; 26: 192-8.
25. OBREJA O, RATHEE PK, LIPS KS, DISTLER C, KRESS M: IL-1 beta potentiates heat-activated currents in rat sensory neurons: involvement of IL-1RI, tyrosine kinase, and protein kinase C. *FASEB J* 2002; 16: 1497-503.
26. EBBINGHAUS M, UHLIG B, RICHTER F *et al*.: The role of interleukin-1beta in arthritic pain: main involvement in thermal, but not mechanical, hyperalgesia in rat antigen-induced arthritis. *Arthritis Rheum* 2012; 64: 3897-907.
27. SCHETT G: Physiological effects of modulating the interleukin-6 axis. *Rheumatology* (Oxford) 2018; 57: ii43-ii50.
28. DE JONGH RF, VISSERS KC, MEERT TF, BOOIJ LH, DE DEYNE CS, HEYLEN RJ: The role of interleukin-6 in nociception and pain. *Anesth Analg* 2003; 96: 1096-103.
29. XU XJ, HAO JX, ANDELL-JONSSON S, POLI V, BARTFAI T, WIESENFELD-HALLIN Z: Nociceptive responses in interleukin-6-deficient mice to peripheral inflammation and peripheral nerve section. *Cytokine* 1997; 9: 1028-33.
30. ANDRATSCH M, MAIR N, CONSTANTIN CE *et al*.: A key role for gp130 expressed on peripheral sensory nerves in pathological pain. *J Neurosci* 2009; 29: 13473-83.
31. OBREJA O, BIASIO W, ANDRATSCH M *et al*.: Fast modulation of heat-activated ionic current by proinflammatory interleukin 6 in rat sensory neurons. *Brain* 2005; 128: 1634-41.
32. VON BANCHET GS, KIEHL M, SCHAIBLE HG: Acute and long-term effects of IL-6 on cultured dorsal root ganglion neurones from adult rat. *J Neurochem* 2005; 94: 238-48.
33. FARGHALY HS, MAHMOUD AM, ABDEL-SATER KA: Effect of dexmedetomidine and cold stress in a rat model of neuropathic pain: Role of interleukin-6 and tumor necrosis factor-alpha. *Eur J Pharmacol* 2016; 776: 139-45.
34. BIAN C, WANG ZC, YANG JL, LU N, ZHAO ZQ, ZHANG YQ: Up-regulation of interleukin-23 induces persistent allodynia via CX3CL1 and interleukin-18 signaling in the rat spinal cord after tetanic sciatic stimulation. *Brain Behav Immun* 2014; 37: 220-30.
35. SIEPER J, PODDUBNYY D, MIOSSEC P: The IL-23-IL-17 pathway as a therapeutic target in axial spondyloarthritis. *Nat Rev Rheumatol* 2019; 15: 747-57.
36. CHANG SH, PARK H, DONG C: Act1 adaptor protein is an immediate and essential signaling component of interleukin-17 receptor. *J Biol Chem* 2006; 281: 35603-7.
37. HU Y, OTA N, PENG I *et al*.: IL-17RC is required for IL-17A- and IL-17F-dependent signaling and the pathogenesis of experimental autoimmune encephalomyelitis. *J Immunol* 2010; 184: 4307-16.
38. NOVATCHKOVA M, LEIBBRANDT A, WERZOWA J, NEUBUSER A, EISENHABER F: The STIR-domain superfamily in signal transduction, development and immunity. *Trends Biochem Sci* 2003; 28: 226-9.
39. QIAN Y, LIU C, HARTUPEE J *et al*.: The adaptor Act1 is required for interleukin 17-dependent signaling associated with autoimmune and inflammatory disease. *Nat Immunol* 2007; 8: 247-56.
40. TOY D, KUGLER D, WOLFSON M *et al*.: Cutting edge: interleukin 17 signals through a heteromeric receptor complex. *J Immunol* 2006; 177: 36-9.
41. WRIGHT JF, BENNETT F, LI B *et al*.: The human IL-17F/IL-17A heterodimeric cytokine signals through the IL-17RA/IL-17RC receptor complex. *J Immunol* 2008; 181: 2799-805.
42. ASKARI A, NAGHIZADEH MM, HOMAYOUNFAR R *et al*.: Increased serum levels of IL-17A and IL-23 are associated with decreased vitamin D3 and increased pain in osteoarthritis. *PLoS One* 2016; 11: e0164757.
43. SEGOND VON BANCHET G, BOETTGER MK, KONIG C, IWAKURA Y, BRAUER R, SCHAIBLE HG: Neuronal IL-17 receptor upregulates TRPV4 but not TRPV1 receptors in DRG neurons and mediates mechanical but not thermal hyperalgesia. *Mol Cell Neurosci* 2013; 52: 152-60.
44. PINTO LG, CUNHA TM, VIEIRA SM *et al*.: IL-17 mediates articular hypernociception in antigen-induced arthritis in mice. *Pain* 2010; 148: 247-56.
45. KIM CF, MOALEM-TAYLOR G: Interleukin-17 contributes to neuroinflammation and neuropathic pain following peripheral nerve injury in mice. *J Pain* 2011; 12: 370-83.
46. EBBINGHAUS M, NATURA G, SEGOND VON BANCHET G *et al*.: Interleukin-17A is involved in mechanical hyperalgesia but not in the severity of murine antigen-induced arthritis. *Sci Rep* 2017; 7: 10334.
47. LUO X, TAI WL, SUN L *et al*.: Crosstalk between astrocytic CXCL12 and microglial CXCR4 contributes to the development of neuropathic pain. *Mol Pain* 2016; 12.
48. NUMMENMAA E, HAMALAINEN M, MOILANEN LJ *et al*.: Transient receptor potential ankyrin 1 (TRPA1) is functionally expressed in primary human osteoarthritic chondrocytes. *Arthritis Res Ther* 2016; 18: 185.
49. O'SHEA JJ, SCHWARTZ DM, VILLARINO AV, GADINA M, MCINNES IB, LAURENCE A: The JAK-STAT pathway: impact on human disease and therapeutic intervention. *Annu Rev Med* 2015; 66: 311-28.
50. STRAND V, DE VLAM K, COVARRUBIAS-COBOS JA *et al*.: Effect of tofacitinib on patient-reported outcomes in patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors in the phase III, randomised controlled trial: OPAL Beyond. *RMD Open* 2019; 5: e000808.
51. STRAND V, KREMER JM, GRUBEN D, KRISHNASWAMI S, ZWILLICH SH, WALLENSTEIN GV: Tofacitinib in combination with conventional disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: patient-reported outcomes from a phase III randomized controlled trial. *Arthritis Care Res* (Hoboken) 2017; 69: 592-8.
52. DOMINGUEZ E, MAUBORGNE A, MALLET J, DESCLAUX M, POHL M: SOCS3-mediated blockade of JAK/STAT3 signaling pathway reveals its major contribution to spinal cord neuroinflammation and mechanical allodynia after peripheral nerve injury. *J Neurosci* 2010; 30: 5754-66.
53. TSUDA M, KOHRO Y, YANO T *et al*.: JAK-STAT3 pathway regulates spinal astrocyte proliferation and neuropathic pain maintenance in rats. *Brain* 2011; 134: 1127-39.
54. LI YY, LI H, LIU ZL *et al*.: Activation of STAT3-mediated CXCL12 up-regulation in the dorsal root ganglion contributes to oxaliplatin-induced chronic pain. *Mol Pain* 2017; 13: 1744806917747425.
55. WAN J, DING Y, TAHIR AH *et al*.: Electroacupuncture attenuates visceral hypersensitivity by inhibiting JAK2/STAT3 signaling pathway in the descending pain modulation system. *Front Neurosci* 2017; 11: 644.
56. WANG C, SONG Y, WANG X, MAO R, SONG L: Baicalin ameliorates collagen-induced arthritis through the suppression of Janus kinase 1 (JAK1)/signal transducer and activator of transcription 3 (STAT3) signaling in mice. *Med Sci Monit* 2018; 24: 9213-22.
57. WEI JY, LIU CC, OUYANG HD *et al*.: Activation of RAGE/STAT3 pathway by methylglyoxal contributes to spinal central sensitization and persistent pain induced by bortezomib. *Exp Neurol* 2017; 296: 74-82.
58. ZHANG XS, LI X, LUO HJ *et al*.: Activation of the RAGE/STAT3 pathway in the dorsal root ganglion contributes to the persistent pain hypersensitivity induced by lumbar disc herniation. *Pain Physician* 2017; 20: 419-27.
59. LIU S, MI WL, LI Q *et al*.: Spinal IL-33/ST2 Signaling contributes to neuropathic pain via neuronal CaMKII-CREB and astroglial JAK2-STAT3 cascades in mice. *Anesthesiology* 2015; 123: 1154-69.
60. LI CD, ZHAO JY, CHEN JL *et al*.: Mechanism of the JAK2/STAT3-CAV-1-NR2B signaling pathway in painful diabetic neuropathy. *Endocrine* 2019; 64: 55-66.
61. ZHONG L, FU K, XIAO W, WANG F, SHEN LL: Overexpression of miR-98 attenuates neuropathic pain development via targeting STAT3 in CCI rat models. *J Cell Biochem* 2018 Nov 28 [Online ahead of print].
62. HU F, CUI Y, GUO R *et al*.: Spinal leptin contributes to the development of morphine antinociceptive tolerance by activating the STAT3-NMDA receptor pathway in rats. *Mol Med Rep* 2014; 10: 923-30.
63. DING HH, ZHANG SB, LV YY *et al*.: TNF-alpha/STAT3 pathway epigenetically upregulates Nav1.6 expression in DRG and contributes to neuropathic pain induced by L5-VRT. *J Neuroinflammation* 2019; 16: 29.
64. LIU CC, HUANG ZX, LI X *et al*.: Upregulation of NLRP3 via STAT3-dependent histone acetylation contributes to painful neuropathy induced by bortezomib. *Exp Neurol* 2018; 302: 104-11.
65. WANG B, LIU S, FAN B *et al*.: PKM2 is involved in neuropathic pain by regulating ERK and STAT3 activation in rat spinal cord. *J Headache Pain* 2018; 19: 7.
66. CAPORALI R, ZAVAGLIA D: Real-world experience with tofacitinib for the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2019; 37: 485-95.
67. DHILLON S: Tofacitinib: a review in rheumatoid arthritis. *Drugs* 2017; 77: 1987-2001.
68. AL-SALAMA ZT, SCOTT LJ: Baricitinib: a review in rheumatoid arthritis. *Drugs* 2018; 78: 761-72.
69. STRAND V, LEE EB, FLEISCHMANN R *et al*.: Tofacitinib versus methotrexate in rheumatoid arthritis: patient-reported outcomes from

the randomised phase III ORAL Start trial. *RMD Open* 2016; 2: e000308.

70. STRAND V, VAN DER HEIJDE D, TANAKA Y *et al*.: Tofacitinib in combination with methotrexate in patients with rheumatoid arthritis: patient-reported outcomes from the 24-month Phase 3 ORAL Scan study. *Clin Exp Rheumatol* 2020; 38: 848-57.
71. STRAND V, VAN VOLLENHOVEN RF, LEE EB *et al*.: Tofacitinib or adalimumab versus placebo: patient-reported outcomes from a phase 3 study of active rheumatoid arthritis. *Rheumatology* (Oxford) 2016; 55: 1031-41.
72. STRAND V, BURMESTER GR, ZERBINI CA *et al*.: Tofacitinib with methotrexate in third-line treatment of patients with active rheumatoid arthritis: patient-reported outcomes from a phase III trial. *Arthritis Care Res* (Hoboken) 2015; 67: 475-83.
73. STRAND V, KREMER J, WALLENSTEIN G *et al*.: Effects of tofacitinib monotherapy on patient-reported outcomes in a randomized phase 3 study of patients with active rheumatoid arthritis and inadequate responses to DMARDs. *Arthritis Res Ther* 2015; 17: 307.
74. STRAND V, DE VLAM K, COVARRUBIAS-COBOS JA *et al*.: Tofacitinib or adalimumab versus placebo: patient-reported outcomes from OPAL Broaden-a phase III study of active psoriatic arthritis in patients with an inadequate response to conventional synthetic disease-modifying antirheumatic drugs. *RMD Open* 2019; 5: e000806.
75. TAYLOR PC: Understanding mediators of pain reduction in psoriatic arthritis patients treated with tofacitinib: role of inflammation. Poster presented at EULAR 2019. Jun 12-15, 2019, Madrid. 2019.
76. DOUGADOS M: The effect of tofacitinib on residual pain in patients with psoriatic arthritis. Abstract presented at ACR 2019. Atlanta GA, USA. November 9-13, 2019. .
77. TAYLOR PC, LEE YC, FLEISCHMANN R *et al*.: Achieving pain control in rheumatoid arthritis with baricitinib or adalimumab plus methotrexate: results from the RA-BEAM trial. *J Clin Med* 2019; 8: 831.
78. FAUTREL B, ZHU B, TAYLOR PC *et al*.: Comparative effectiveness of improvement in pain and physical function for baricitinib versus adalimumab, tocilizumab and tofacitinib monotherapies in rheumatoid arthritis patients who are naive to treatment with biologic or conventional synthetic disease-modifying antirheumatic drugs: a matching-adjusted indirect comparison. *RMD Open* 2020; 6.