Rheumatol Ther (2022) 9:1451–1464
https://doi.org/10.1007/s40744-022-00482-5

ORIGINAL RESEARCH

Identifying and Quantifying the Role of Inflammation in Pain Reduction for Patients With Psoriatic Arthritis Treated With Tofacitinib: A Mediation Analysis

Kurt de Vlam · Philip J. Mease · Andrew G. Bushmakin · Roy Fleischmann · Alexis Ogdie · Valderilio F. Azevedo · Joseph F. Merola · John Woolcott · Joseph C. Cappelleri · Lara Fallon · Peter C. Taylor

Received: February 7, 2022 / Accepted: August 1, 2022 / Published online: September 8, 2022

ABSTRACT

Introduction: Pain is a multidimensional factor and core domain of psoriatic arthritis (PsA). This analysis aimed to quantify the role of potential inflammation-associated outcomes on pain reduction in patients with PsA receiving tofacitinib, using mediation modeling.

Methods: Pooled data were from two phase 3 studies (OPAL Broaden and OPAL Beyond) of patients with active PsA treated with tofacitinib 5 mg twice daily or placebo. Mediation modeling was utilized to quantify the indirect effects (via Itch Severity Item [ISI], C-reactive protein [CRP] levels, swollen joint count [SJC], Psoriasis Area and Severity Index [PASI], and enthesitis [using Leeds Enthesitis Index]) and direct effects (representing all other factors) of tofacitinib treatment on pain improvement.

Results: The initial model showed that tofacitinib treatment affects pain, primarily indirectly, via ISI, CRP, SJC, PASI, and enthesitis (overall 84.0%; $P = 0.0009$), with 16.0% ($P = 0.5274$) attributable to the direct effect. The model was respecified to exclude SJC and PASI. Analysis of the final model revealed that 29.5% ($P = 0.0579$) of tofacitinib treatment effect on pain was attributable to the direct effect, and 70.5% ($P < 0.0001$) was attributable to the indirect effect. ISI, CRP, and enthesitis mediated 37.4% ($P = 0.0002$), 15.3% ($P = 0.0107$), and 17.8% ($P = 0.0157$) of the tofacitinib treatment effect on pain, respectively.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40744-022-00482-5.

K. de Vlam
Department of Rheumatology, University Hospitals Leuven, Leuven, Belgium

P. J. Mease
Swedish Medical Center, University of Washington, Seattle, WA, USA

A. G. Bushmakin · J. C. Cappelleri
Pfizer Inc, Groton, CT, USA

R. Fleischmann
Metroplex Clinical Research Center, University of Texas Southwestern Medical Center, Dallas, TX, USA

A. Ogdie
Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

V. F. Azevedo
Universidade Federal do Paraná, Curitiba, Brazil

J. F. Merola
Division of Rheumatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

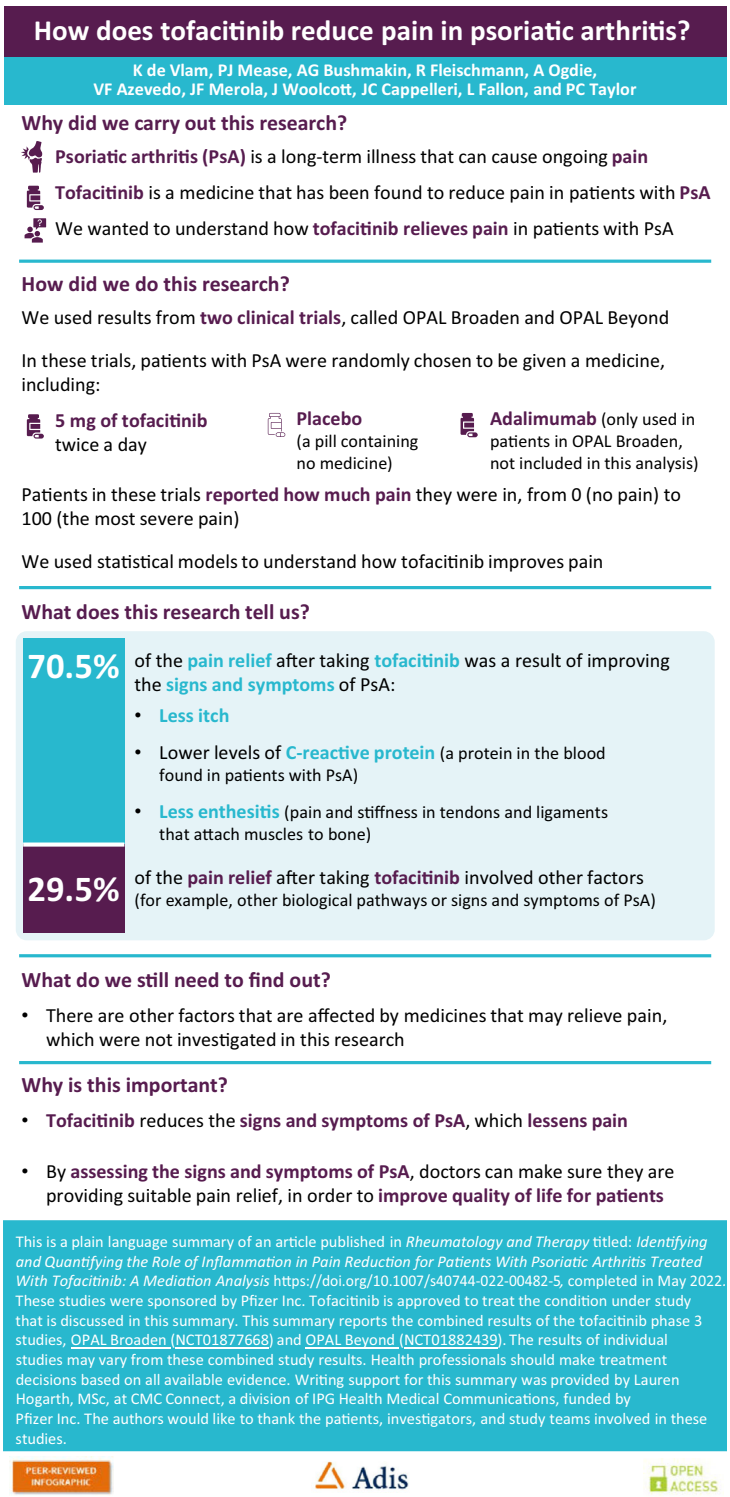
J. Woolcott
Pfizer Inc, Collegeville, PA, USA

L. Fallon (✉)
Pfizer Inc, Kirkland, Montreal, QC, Canada
e-mail: lara.fallon@pfizer.com

P. C. Taylor
University of Oxford, Oxford, UK

Conclusions: The majority of the effect of tofacitinib on pain was collectively mediated by itch, CRP, and enthesitis, with itch being the primary mediator of treatment effect.**Trial Registration**: NCT01877668, NCT01882439.

Graphical PLS:



Keywords: Inflammation; Pain; Psoriatic arthritis; Tofacitinib

Key Summary Points

Why carry out this study?

Pain is a common symptom of psoriatic arthritis (PsA), and it is considered a highly important treatment outcome among patients and physicians.

To our knowledge, mediation modeling (a statistical methodology used to explain the mechanisms underlying an observed relationship between independent and dependent variables via other explanatory variables, termed mediators) has not previously been used to investigate the relationship between pain and inflammation-associated mediators in patients with PsA treated with tofacitinib.

What was learned from the study?

Inflammation was identified as a significant mediator of the overall treatment effect on pain in tofacitinib-treated patients with PsA.

The majority of the effect (70.5%) of tofacitinib on pain was collectively mediated by itch, C-reactive protein, and enthesitis, with itch being identified as the main mediator of treatment effect (37.4% in the final respecified mediation model).

These results highlight the importance of assessing these signs and symptoms in clinical practice, and selecting treatment accordingly, in order to facilitate the treatment of pain and increase the quality of life of patients with PsA.

DIGITAL FEATURES

This article is published with digital features, including a graphical plain language summary, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.20401938.

INTRODUCTION

Psoriatic arthritis (PsA) affects approximately 30% of patients with psoriasis [1]. Patients with PsA often experience progressive joint damage [2], and the disease can involve skin inflammation, peripheral joint disease, axial disease, enthesitis, and dactylitis [3]. Pain is a common symptom of PsA [4], and it is considered a core domain and a highly important treatment outcome for both patients and physicians [5, 6].

Clinically, pain can be categorized into three types: nociceptive, nociplastic, and neuropathic. The pain associated with the primary dermatologic (skin inflammation) and rheumatic (joint inflammation and destruction, axial disease, enthesitis, and dactylitis) manifestations of PsA is typically nociceptive pain [7]. This is transmitted via the activation of specialized afferent sensory neurons, known as nociceptors, which densely innervate the periphery, including tissues, such as skin, synovium, and bone [8]. Activation of nociceptors occurs with actual or potential tissue damage caused by mechanical, chemical, or thermal stimulation, and is often accompanied by the release of pro-inflammatory mediators [8]. However, emerging evidence in PsA and rheumatoid arthritis suggests that not all pain necessarily correlates with inflammatory markers [7, 9], suggesting that noninflammatory mechanisms may contribute.

Nociplastic pain manifests due to the activation of peripheral nociceptors, despite the absence of damage to the somatosensory nervous system and without the presence of actual or potential tissue damage [10]. This type of pain is reportedly caused by a central sensitization mechanism [11, 12], which increases the responsiveness and excitability of nociceptive neurons in the central nervous system and promotes pain hypersensitivity [13]. Studies have demonstrated that up to 42.9% of patients with PsA may have concomitant central sensitization, and these patients have more severe disease activity measures [14, 15] and are less

likely to achieve minimal disease activity, compared with patients without concomitant central sensitization [15].

A third type of pain involved in rheumatic conditions is neuropathic pain, which results from a central pain mechanism [16]. Neuropathic pain is instigated by the presence of a lesion and/or disease in the peripheral or central somatosensory nervous system [17]. The lesion and/or disease is believed to initiate a maladaptive pathophysiological cascade, promoting the sensitization of nociceptors to either noxious or innocuous stimuli [11, 12, 17]. Studies of pain in PsA, using the patient questionnaire PainDETECT [18], have reported that 22–28% of patients appear to demonstrate characteristics of neuropathic pain [7, 19], and it has a substantial impact on quality of life and is associated with poor mental health [19].

As previously described, PsA is a heterogenous disease, and it has an impact on multiple domains [3]. This makes treatment challenging and reduces the patient's quality of life [20]. Quality of life is typically associated with the rheumatologic manifestations of the disease (pain and swelling of joints) [21]; however, evidence in patients with PsA and psoriasis suggests that dermatologic symptoms, particularly itch, also have a substantial impact [5, 22] and may interact with pain [23, 24]. While the sensation of itch is different from pain, the two are intimately intertwined. Patients with moderate to severe psoriasis have described skin pain, itching, burning, and stinging as symptoms [23]. Both itch and pain are transmitted by the somatosensory nervous system, and the release of inflammatory neuropeptides from peripheral nerve endings due to psoriatic skin lesions, external stimuli (e.g., scratching), or psychological stress can further stimulate itch, inflammation, and pain via the release of immunomodulators, such as cytokines [24, 25]. Interestingly, involvement of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway has been demonstrated in clinical studies in which the JAK inhibitor tofacitinib relieved symptoms of itch and pain [26, 27].

Tofacitinib is an oral JAK inhibitor approved for the treatment of PsA. In patients with PsA, the efficacy and safety of tofacitinib 5 and 10 mg twice daily (BID), in combination with a conventional synthetic disease-modifying antirheumatic drug (csDMARD), have been described in two phase 3, randomized, placebo-controlled, double-blind trials of up to 12 months (OPAL Beyond and OPAL Broaden) [28, 29] and in an open-label, long-term extension study of up to 48 months (OPAL Balance) [30]. Tofacitinib has been associated with greater improvements from baseline in pain Visual Analog Scale (VAS) score, starting at week 2 (the first post-baseline assessment), and a higher proportion of patients achieved greater than or equal to minimum clinically important differences in pain, compared with placebo [31–33].

This post hoc analysis used mediation modeling to identify and quantify the role of inflammation-associated mediators, including patient-reported itch, C-reactive protein (CRP) levels, swollen joint count (SJC), Psoriasis Area and Severity Index (PASI), and enthesitis, in pain reduction in patients with PsA treated with tofacitinib. To our knowledge, this is one of the first studies to use mediation modeling to investigate the relationship between pain and inflammation in patients with PsA.

METHODS

Study Design and Patients

This analysis included data collected from two randomized, placebo-controlled, double-blind, phase 3 studies of patients with active PsA. OPAL Broaden (12 months' duration, NCT01877668) enrolled patients who had an inadequate response (IR) to $\geq$ 1 csDMARD and who were tumor necrosis factor inhibitor (TNFi)-naïve [28]. Patients were randomized to receive tofacitinib 5 mg BID, tofacitinib 10 mg BID, adalimumab 40 mg subcutaneous once every 2 weeks (active control arm), or placebo advancing to tofacitinib 5 or 10 mg BID at month 3 [28]. OPAL Beyond (6 months' duration, NCT01882439) enrolled patients who had an IR to $\geq$ 1 TNFi [29]. Patients were randomized to receive tofacitinib 5 mg BID, tofacitinib

10 mg BID, or placebo advancing to tofacitinib 5 or 10 mg BID at Month 3 [29]. All patients continued on a stable dose of a single csDMARD [28, 29]. The current analysis focuses on those patients treated with tofacitinib 5 mg BID (the approved dose for PsA) and placebo. Patients treated with tofacitinib 10 mg BID or with adalimumab were not included in the analysis.

Both studies were conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the principles of the Declaration of Helsinki, and they were approved by the relevant institutional review board or independent ethics committee at each investigational site [28, 29]. All patients provided written informed consent. No further ethical approval was required for this post hoc analysis in accordance with the policies of our institutions.

Pain and Mediators of Inflammation

Pain was evaluated using the Patient's Assessment of Arthritis Pain, a VAS ranging from 0 to 100 mm, where higher values indicate more severe patient pain. Inflammation-associated mediators selected for this model were as follows: patient-reported Itch Severity Item (ISI; scores ranging from 0 to 10, with higher scores indicating more severe itching); CRP levels; SJC (out of 66 joints); PASI (scores ranging from 0 to 72, with higher scores indicating more severe disease); enthesitis, measured by Leeds Enthesitis Index (LEI; scores ranging from 0 to 6, with higher scores indicating more affected sites) or Spondyloarthritis Research Consortium of Canada Enthesitis Index (SPARCC; scores ranging from 0 to 16, with higher scores indicating more affected sites).

Initial Mediation Model

Mediation modeling is a statistical methodology that seeks to explain mechanisms underlying an observed relationship between independent and dependent variables via other explanatory variables, termed mediators [34]. The objective of mediation modeling is to determine the extent to which the effect of an independent variable (e.g., tofacitinib relative to placebo) on a dependent variable (e.g., pain) is indirect, via identified mediators, or direct, which captures all other effects [34].

Analyses were performed to model data pooled from the TNFi-naïve and TNFi-IR patient populations from OPAL Broaden and OPAL Beyond, respectively. In the initial mediation model, treatment (tofacitinib 5 mg BID versus placebo) was defined as the independent binary variable; pain (VAS score) was defined as the dependent variable, and inflammation (ISI, CRP, SJC, PASI, and enthesitis [LEI]) was defined as the mediator (Fig. 1). Pain, ISI, CRP, SJC, PASI, and LEI scores used in the model were means of all available data, at patient level, from months 1 and 3 in OPAL Beyond and OPAL Broaden.

In the initial model, the effect of tofacitinib treatment on pain, which was mediated via inflammation (ISI, CRP, SJC, PASI, and LEI), was designated as an indirect effect, and treatment effect on pain not mediated by ISI, CRP, SJC, PASI, and LEI (i.e., the impact of all other factors) was designated as a direct effect. The total effect of treatment on pain was the sum of the indirect and direct effects (Fig. 1). Based on the results of the initial model, the mediation model can be respecified to resolve any inconsistencies that occur.

RESULTS

Patients

Of 474 patients treated with tofacitinib 5 mg BID and placebo in OPAL Broaden and OPAL Beyond, the initial model included data from 329 (69.4%) patients who had data on all outcomes used in the modeling. Demographics and baseline disease characteristics were similar across treatment groups for the individual studies and have been presented in full elsewhere [28, 29]; baseline values for the mediators included in the model are shown in Table S1 in the electronic Supplementary Material.

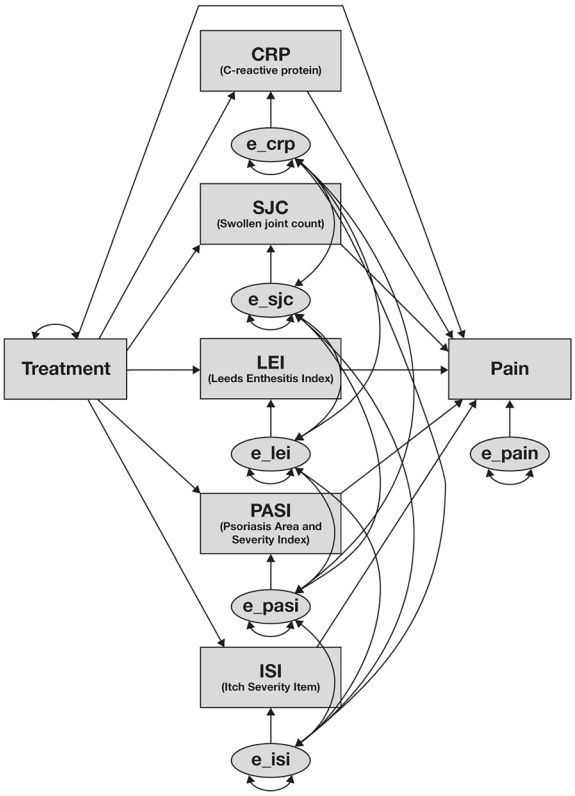


Fig. 1 Initial mediation model. Treatment (variable "Treatment") is represented by a binary variable (tofacitinib 5 mg BID versus placebo). Pain (variable "Pain") was measured by Patient's Assessment of Arthritis Pain (VAS). Inflammation was measured by ISI (variable "ISI"), CRP (variable "CRP"), SJC (variable "SJC"), PASI (variable "PASI"), and enthesitis (measured by LEI [variable "LEI"]). Variables e_pain, e_crp, e_sjc, e_lei, e_pasi, and e_isi represent error terms. *Curved two-headed arrows* between error terms represent covariances. *Curved two-headed arrows* pointing to the same variable represent variance. *BID* twice daily, *CRP* C-reactive protein, *ISI* Itch Severity Item, *LEI* Leeds Enthesitis Index, *PASI* Psoriasis Area and Severity Index, *SJC* swollen joint count (out of 66 joints), *VAS* Visual Analog Scale

Initial Mediation Model

In the analyses of pooled data from OPAL Broaden (TNFi-naïve patients) and OPAL Beyond (TNFi-IR patients), the proportion of the direct effect of tofacitinib treatment on pain was 16.0% ($P = 0.5274$; Fig. 2). The model demonstrates that tofacitinib predominantly mediates pain indirectly via ISI, CRP, SJC, PASI, and enthesitis (LEI) (overall 84.0%; $P = 0.0009$). The largest indirect effect of the treatment on pain was via ISI (64.4%; $P = 0.0035$). The indirect effects of the treatment on pain via SJC (< 0.1%; $P = 0.9929$), LEI (9.5%; $P = 0.2220$), and PASI (− 14.4%; $P = 0.0979$) were not significant. The negative estimate for PASI, while not significant, suggests that worsening of the PASI score leads to improvement in pain; thus, keeping PASI as a mediator may therefore lead to a mis-specified model. Correlations between variables included in this model are displayed in Table S2 in the electronic Supplementary Material.

Respecified Mediation Model

The initial mediation model was respecified to exclude the path via SJC due to its numerically negligible value, and the path via PASI, which was contradictory (Fig. 3). The independent and dependent variables remained the same as in the initial model.

Fewer mediators were included in the respecified model (ISI, CRP, and enthesitis) compared with the initial model and, as a result, more patients had available data for all mediators and were able to be included in this model. As such, 468 (98.7%) of the 474 patients who received tofacitinib 5 mg BID and placebo in OPAL Broaden and OPAL Beyond were included. In the respecified model, 29.5% ($P = 0.0579$) of the effect of tofacitinib on pain was a result of the direct effect, and 70.5% ($P < 0.0001$) was attributable to the indirect effect (Fig. 4). The largest indirect effect of tofacitinib treatment on pain was mediated by ISI (37.4%; $P = 0.0002$), followed by enthesitis represented by LEI (17.8%; $P = 0.0157$), and CRP (15.3%; $P = 0.0107$) (Fig. 4). LEI and SPARCC are highly correlated (Pearson correlation coefficient $r = 0.89$ [$P < 0.0001$]). Thus, the respecified model was also assessed using SPARCC as the measure of enthesitis in a sensitivity analysis and yielded results that were consistent with when LEI was used as the measure of enthesitis.

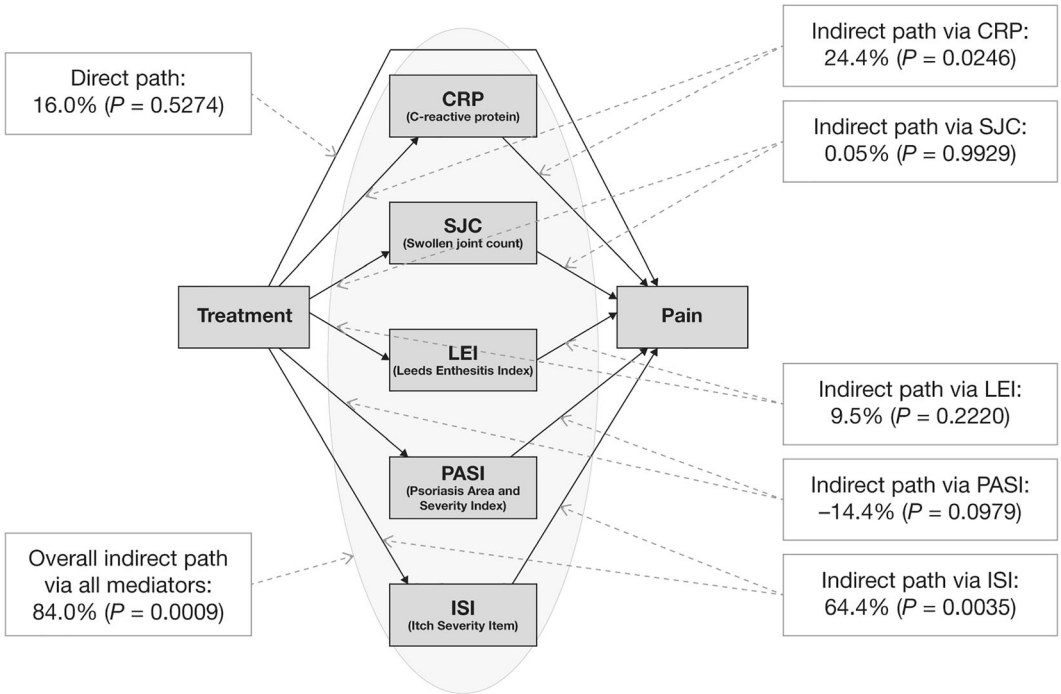


Fig. 2 Mediation effects in the initial model: indirect and direct effects of tofacitinib treatment on pain in patients pooled from OPAL Broaden and OPAL Beyond. Treatment (variable "Treatment") is represented by a binary variable (tofacitinib 5 mg BID versus placebo). Pain (variable "Pain") was measured by Patient's Assessment of Arthritis Pain (VAS). Inflammation was measured by ISI (variable "ISI"), CRP (variable "CRP"), SJC (variable "SJC"), PASI (variable "PASI"), and enthesitis (measured by LEI [variable "LEI"]) at months 1 and 3. *BID* twice daily, *CRP* C-reactive protein, *ISI* Itch Severity Item, *LEI* Leeds Enthesitis Index, *PASI* Psoriasis Area and Severity Index, *SJC* swollen joint count (out of 66 joints), *VAS* Visual Analog Scale

DISCUSSION

This analysis aimed to identify and quantify the role of inflammation in the effect of tofacitinib treatment on reducing pain in patients with PsA. Using mediation modeling, inflammation was identified as a significant mediator of the overall treatment effect on pain in tofacitinib-treated patients with PsA. The initial mediation model was respecified to exclude the path via SJC, which was numerically negligible, and the path via PASI, which was contradictory. The very small correlation between PASI and pain ($r = 0.11$) could have contributed to this illogical result. In the final respecified mediation model of pooled data from OPAL Broaden and OPAL Beyond, the majority of the treatment effect (70.5%) of tofacitinib on pain was collectively mediated by itch, CRP, and enthesitis, with itch, as measured by ISI, identified as the main mediator of treatment effect (37.4%).

The JAK/STAT signaling cascade has been implicated as a fundamental transduction pathway, directly modulating the nociceptive response in spondyloarthritides via release of pro- and anti-inflammatory cytokines [35, 36]. In PsA, pro-inflammatory cytokines are released into the synovium and within the epidermis through activation of the JAK/STAT pathway and the STAT-dependent interleukin (IL)-23/IL-17 axis [36, 37]. Evidence from models of inflammatory arthritis suggests that these pro-inflammatory cytokines stimulate nociceptive sensory nerve fibers in the periphery and elicit a pain response [36–38]. The IL-23/IL-17 axis has been firmly implicated in the pathogenesis of PsA, and dysregulation of this signaling cascade is believed to promote the painful

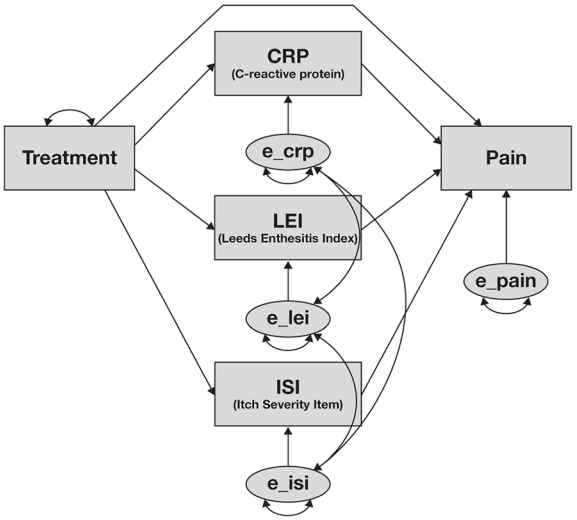


Fig. 3 Respecified mediation model. Treatment (variable "Treatment") is represented by a binary variable (tofacitinib 5 mg BID versus placebo). Pain (variable "Pain") was measured by Patient's Assessment of Arthritis Pain (VAS). Inflammation was measured by ISI (variable "ISI"), CRP (variable "CRP"), and enthesitis (measured by LEI [variable "LEI"]). Variables e_pain, e_isi e_crp, and e_lei represent error terms. *Curved two-headed arrows* between error terms represent covariances. *Curved two-headed arrows* pointing to the same variable represent variance. *ID* twice daily, *CRP* C-reactive protein, *ISI* Itch Severity Item, *LEI* Leeds Enthesitis Index, *VAS* Visual Analog Scale

rheumatologic and dermatologic symptoms reported by patients [39–42]. Indeed, increased systemic expression of IL-23 has been hypothesized to drive significant entheseal inflammation in peripheral and axial locations via the local upregulation of the cytokines IL-17, IL-6, and IL-22 [40]. Additionally, IL-23 drives the psoriatic skin phenotype by activating the release of inflammatory T-cells, IL-17, IL-22, and TNFα, which promotes the activation and proliferation of keratinocytes [38, 42] and is believed to be associated with the sensation of itch on the affected skin [24, 43]. Interestingly, a study investigating the molecular mechanisms underlying tofacitinib efficacy in patients with psoriasis reported that treatment with tofacitinib promoted robust attenuation of JAK/STAT signaling in keratinocytes on day 1, resulting in reductions in keratinocyte proliferation, elimination of pro-inflammatory keratinocyte cytokine signaling, and inhibition of the IL-23/IL-17 pathway by week 4 [38]. These data are consistent with the results of the current study, which suggests that tofacitinib mediates its effect on pain via itch in patients with PsA. Correspondingly, the data presented here also identified a mediation effect by enthesitis, as measured by LEI and SPARCC. While there are few studies describing the mechanism of action of tofacitinib on enthesitis, it is likely that tofacitinib ameliorates pain via reductions in enthesitis-associated inflammatory nociceptive pain, mediated by reductions in local IL-23/IL-17 signaling, as previously discussed [40]. However, it should be noted that while IL-23 signals via the pairing of JAK2/tyrosine kinase 2 [42], the inhibitory effects of tofacitinib are thought to be predominantly through JAK1 and JAK3 [38]. Further research is required to understand whether clinical benefits of tofacitinib are a consequence of direct inhibition of the IL-23/IL-17 pathway or whether such modulation is downstream of other cytokines directly inhibited by tofacitinib.

This study identified itch as the main mediator of pain in patients receiving tofacitinib, suggesting that itch may be a key mediator of pain in patients with PsA. Although itch and pain appear to be independent sensations, evidence suggests that their neural mechanisms are linked and that they may share certain mediators and receptors [44]. Though the neurobiological relationship between itch and pain remains incompletely understood, investigations examining the molecular pathways regulating psoriatic dermatologic manifestations have suggested that dysfunctional nociceptive neurons may promote itch, discomfort, and hyperalgesia in patients with psoriasis [45]. Indeed, patients with psoriasis demonstrate enhanced pain sensitivity to pressure, cold, and heat in itchy skin, compared with unaffected skin or healthy individuals [45–47], suggesting that alterations in signal transmission by nociceptive neurons may promote hyperalgesia. Correspondingly, psoriatic skin displays an overexpression of thermosensitive transient receptor potential (TRP) channels [43], with TRPV1 playing an essential role in transduction inflammation, as well as having a role in itch

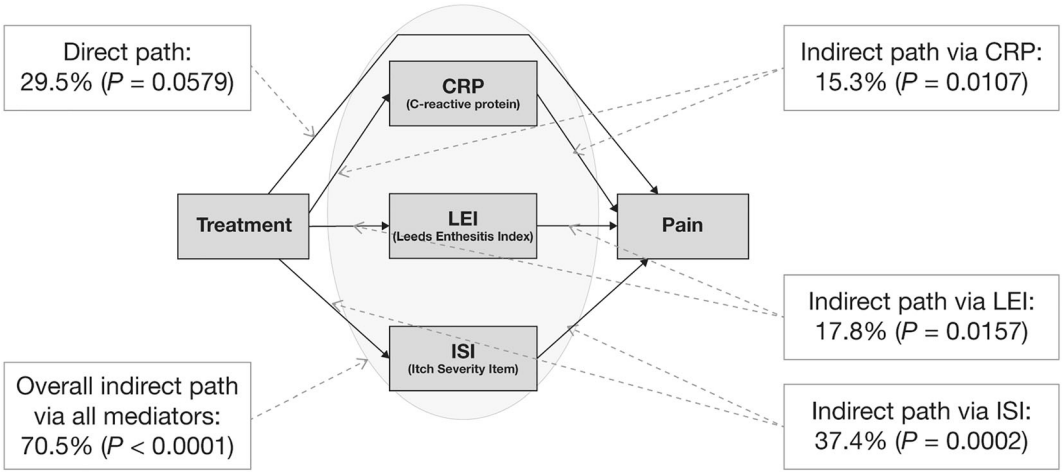


Fig. 4 Mediation effects in the respecified model: indirect and direct effects of tofacitinib treatment on pain in patients pooled from OPAL Broaden and OPAL Beyond. Treatment (variable "Treatment") is represented by a binary variable (tofacitinib 5 mg BID versus placebo). Pain (variable "Pain") was measured by Patient's Assessment of Arthritis Pain (VAS). Inflammation was measured by ISI (variable "ISI"), CRP (variable "CRP"), and enthesitis (measured by LEI [variable "LEI"]) at months 1 and 3. *BID* twice daily, *CRP* C-reactive protein, *ISI* Itch Severity Item, *LEI* Leeds Enthesitis Index, *VAS* Visual Analog Scale

[43, 48]; pharmacologic ablation of this channel ameliorates inflammation [48]. Interestingly, the upregulation of TRPV1 receptors on sensory neurons appears to be dependent on activation of the JAK/STAT signaling cascade [49, 50]. Thus, consistent with the results of this study, it appears that the JAK/STAT pathway may be a common modulator regulating both itch and pain in patients with PsA. On the other hand, it may be that some component of the pathway between itch and pain is occurring through central sensitization in patients with generally increased symptom burden [11, 12]. Treatment of components of pain or swelling may likewise improve the patient's overall well-being and symptom burden.

While the molecular mediators governing the relationship between itch and pain require further investigation, studies have begun to examine the impact of itch on patient-reported outcomes in those with psoriasis. Emerging evidence has indicated that the Dermatology Life Quality Index (DLQI) is strongly and significantly correlated with ISI in patients with psoriasis [27]. Additionally, phase 3 studies investigating the efficacy of tofacitinib in patients with moderate to severe plaque psoriasis have reported rapid (as early as day 2 of treatment) [26] and clinically meaningful improvements (based on change from baseline in ISI score exceeding the clinically important difference determined in the study) in itch with tofacitinib [27], which were associated with a greater proportion of patients achieving improvements in DLQI scores [26]. Therefore, therapies targeting psoriatic skin manifestations to attenuate itch may improve patient quality of life by reducing pain and itch-related discomfort. This highlights the importance of assessing these symptoms in clinical practice and selecting treatment accordingly.

This investigation primarily assessed the impact of tofacitinib treatment on inflammatory nociceptive pain in patients with PsA; however, nociplastic and neuropathic pain present as additional key clinical manifestations of PsA [7, 19], requiring thorough consideration for appropriate pain relief. Although pain is associated with some disease activity metrics, patient-reported pain does not necessarily correlate well with measures of inflammation [9], and clinically significant pain has been reported to persist despite low disease activity scores in patients with PsA [51]. Mental and emotional

factors may also contribute to pain; indeed, depression has been observed to have a small bidirectional relationship with pain in patients with PsA. This means that although depression may sometimes develop as a consequence of pain, it could also increase sensitivity to pain and lower pain threshold [52].

This analysis had some limitations, predominantly the sole use of ISI, PASI, LEI, SPARCC, CRP, and SJC to define inflammation. Using other inflammatory markers may yield different results and indicate that different proportions of the tofacitinib treatment effect are attributable to improvements in inflammation. Incorporating additional metrics of inflammation, as well as noninflammatory mediators in future models may help to better characterize the pathways of PsA-associated pain, although it should be noted that there are few robust metrics of inflammation in PsA. In addition, testing the model using alternative therapies would provide insight into whether inflammatory mediators demonstrate the same proportion of the effect on pain regardless of treatment, or whether mediator effects vary by the pharmacotherapy mechanism of action. Such insights may have implications for disease management, challenging the treat-to-target concept, which assumes that the generic features of inflammation will respond similarly to different treatments that result in comparable improvements in composite scores of disease activity, irrespective of mechanisms of action. Furthermore, while our conclusions are based on the assumptions that our mediation model is correctly specified, it should be emphasized that mediation models in general, like other techniques, cannot prove causation, but rather are hypothesis generating. Correspondingly, the purpose of our mediation modeling was to determine whether our hypothesized causal inferences were harmonious with the data, and to confirm that the validity of the assumptions was not contradicted.

CONCLUSIONS

In conclusion, these results suggest that inflammation may be a significant mediator of the overall effect of tofacitinib on pain relief in patients with PsA. The majority of the effect of tofacitinib on pain was collectively mediated by itch, CRP, and enthesitis, with itch being the primary mediator of treatment effect. Other potential mediators need to be identified to better understand the treatment effect of tofacitinib on pain.

ACKNOWLEDGEMENTS

Funding. This study was sponsored by Pfizer Inc. Medical writing support was funded by Pfizer Inc. Pfizer Inc contributed to the conception/design of the study, data acquisition and analyses, and data interpretation. The journal's Rapid Service Fee for this article was also funded by Pfizer Inc.

Medical Writing, Editorial, and Other Assistance. Medical writing support, under the guidance of the authors, was provided by Laura Graham, PhD, and Lauren Hogarth, MSc, CMC Connect, a division of IPG Health Medical Communications, funded by Pfizer Inc, New York, NY, USA, in accordance with Good Publication Practice (GPP3) guidelines (Ann Intern Med. 2015;163:461–4).

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. KdeV, PJM, AGB, RF, AO, JFM, JW, JCC, LF, and PCT conceived or designed the study, and were involved in data analysis. KdeV, PJM, AGB, RF, JFM, and JCC acquired the data. All authors had access to the data, were involved in the interpretation of the data, reviewed and approved the manuscript's content before submission, and agree to be accountable for all aspects of the work.

Prior Presentation. This manuscript is based on work that has been previously presented in a

poster at EULAR 2020 (Taylor PC et al. Ann Rheum Dis. 2020;79:1724–5 [abstract AB0838]).

Disclosures. Kurt de Vlam has received grant/research support from Celgene, has been a consultant for Eli Lilly, Galapagos NV, Gilead Sciences, Janssen, Novartis, Pfizer Inc, and UCB, and has participated in speakers' bureau for Celgene, Eli Lilly, Janssen, Novartis, Pfizer Inc, and UCB. Philip J Mease has received grant/research support from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Novartis, Pfizer Inc, Sun Pharma, and UCB, has been a consultant for AbbVie, Amgen, Bristol-Myers Squibb, Celgene, CorEvitas, Eli Lilly, Galapagos, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, Novartis, Pfizer Inc, Sun, Pharma and UCB, and has participated in speakers' bureau for AbbVie, Amgen, Janssen, Novartis, Pfizer Inc, and UCB. Andrew G Bushmakin, John Woolcott, Joseph C Cappelleri, and Lara Fallon are employees and shareholders of Pfizer Inc. Roy Fleischmann has received grant/research support from, and has been a consultant for, AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Celltrion, Eli Lilly, Galapagos, Genentech, Gilead Sciences, GlaxoSmithKline, Janssen, Novartis, Noven, Pfizer Inc, Roche, Sanofi-Aventis, UCB, Viela, and VORSO. Alexis Ogdie has received grant/research support from AbbVie, Amgen, Novartis, and Pfizer Inc, and has been a consultant for AbbVie, Amgen, Bristol-Myers Squibb, Celgene, CorEvitas, Eli Lilly, Gilead Sciences, Janssen, Novartis, Pfizer Inc, and UCB. Valderilio F Azevedo has received grant/research support from, and has been a consultant for, AbbVie, Amgen, Fresenius Kabi, GlaxoSmithKline, Janssen, Merck Serono, Novartis, Pfizer Inc, Sandoz, and UCB. Joseph F Merola has been a consultant and/or investigator for AbbVie, Amgen, Biogen, Bristol-Myers Squibb, Dermavant, Eli Lilly, Janssen, Leo Pharma, Novartis, Pfizer Inc, Regeneron, Sanofi, Sun Pharma, and UCB. Peter C Taylor has received grant/research support from Celgene and Galapagos, and has been a consultant for AbbVie, Bristol-Myers Squibb, Biogen, Celltrion, Eli Lilly, Fresenius, Galapagos NV, Gilead Sciences, GlaxoSmithKline, Janssen, Nordic Pharma, Pfizer Inc, Sanofi, and UCB

Compliance with Ethics Guidelines. Both studies were conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the principles of the Declaration of Helsinki, and they were approved by the relevant institutional review board or independent ethics committee at each investigational site [28, 29]. All patients provided written informed consent. No further ethical approval was required for this post hoc analysis in accordance with the policies of our institutions.

Data Availability. Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

REFERENCES

1. Mease PJ, Gladman DD, Papp KA, et al. Prevalence of rheumatologist-diagnosed psoriatic arthritis in patients with psoriasis in European/North

American dermatology clinics. J Am Acad Dermatol. 2013;69:729–35.

2. McHugh NJ, Balachrishnan C, Jones SM. Progression of peripheral joint disease in psoriatic arthritis: a 5-yr prospective study. Rheumatology (Oxford). 2003;42:778–83.

3. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. N Engl J Med. 2017;376:957–70.

4. Kavanaugh A, Helliwell P, Ritchlin CT. Psoriatic arthritis and burden of disease: patient perspectives from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) survey. Rheumatol Ther. 2016;3:91–102.

5. Lebwohl MG, Kavanaugh A, Armstrong AW, Van Voorhees AS. US perspectives in the management of psoriasis and psoriatic arthritis: patient and physician results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) survey. Am J Clin Dermatol. 2016;17: 87–97.

6. Dures E, Hewlett S, Lord J, et al. Important treatment outcomes for patients with psoriatic arthritis: a multisite qualitative study. Patient. 2017;10: 455–62.

7. Rifbjerg-Madsen S, Christensen AW, Christensen R, et al. Pain and pain mechanisms in patients with inflammatory arthritis: a Danish nationwide cross-sectional DANBIO registry survey. PLoS ONE. 2017;12: e0180014.

8. Pinho-Ribeiro FA, Verri WA Jr, Chiu IM. Nociceptor sensory neuron-immune interactions in pain and inflammation. Trends Immunol. 2017;38:5–19.

9. Lee YC, Cui J, Lu B, et al. Pain persists in DAS28 rheumatoid arthritis remission but not in ACR/EULAR remission: a longitudinal observational study. Arthritis Res Ther. 2011;13:R83.

10. Kosek E, Cohen M, Baron R, et al. Do we need a third mechanistic descriptor for chronic pain states? Pain. 2016;157:1382–6.

11. Bailly F, Cantagrel A, Bertin P, et al. Part of pain labelled neuropathic in rheumatic disease might be rather nociplastic. RMD Open. 2020;6: e001326.

12. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain. 2009;10:895–926.

13. Mease PJ. Fibromyalgia, a missed comorbidity in spondyloarthritis: prevalence and impact on assessment and treatment. Curr Opin Rheumatol. 2017;29:304–10.

14. Adami G, Gerratana E, Atzeni F, et al. Is central sensitization an important determinant of functional disability in patients with chronic inflammatory arthritides? Ther Adv Musculoskelet Dis. 2021;13:1759720X21993252.

15. Højgaard P, Ellegaard K, Nielsen SM, et al. Pain mechanisms and ultrasonic inflammatory activity as prognostic factors in patients with psoriatic arthritis: a prospective cohort study. Arthritis Care Res (Hoboken). 2019;71:798–810.

16. Koop SM, ten Klooster PM, Vonkeman HE, Steunebrink LMM, van de Laar MAFJ. Neuropathic-like pain features and cross-sectional associations in rheumatoid arthritis. Arthritis Res Ther. 2015;17: 237.

17. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. Annu Rev Neurosci. 2009;32:1–32.

18. Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin. 2006;22:1911–20.

19. Ramjeeawon A, Choy E. Neuropathic-like pain in psoriatic arthritis: evidence of abnormal pain processing. Clin Rheumatol. 2019;38:3153–9.

20. Mahmood F, Coates LC, Helliwell PS. Current concepts and unmet needs in psoriatic arthritis. Clin Rheumatol. 2018;37:297–305.

21. Gudu T, Gossec L. Quality of life in psoriatic arthritis. Expert Rev Clin Immunol. 2018;14: 405–17.

22. Mrowietz U, Chouela EN, Mallbris L, et al. Pruritus and quality of life in moderate-to-severe plaque psoriasis: post hoc explorative analysis from the PRISTINE study. J Eur Acad Dermatol Venereol. 2015;29:1114–20.

23. Korman NJ, Zhao Y, Li Y, Liao M, Tran MH. Clinical symptoms and self-reported disease severity among patients with psoriasis—implications for psoriasis management. J Dermatol Treat. 2015;26:514–9.

24. Komiya E, Tominaga M, Kamata Y, Suga Y, Takamori K. Molecular and cellular mechanisms of itch in psoriasis. Int J Mol Sci. 2020;21:8406.

25. Choi JE, Di Nardo A. Skin neurogenic inflammation. Semin Immunopathol. 2018;40:249–59.

26. Feldman SR, Thaçi D, Gooderham M, et al. Tofacitinib improves pruritus and health-related quality of life up to 52 weeks: results from 2 randomized phase III trials in patients with moderate to severe

plaque psoriasis. J Am Acad Dermatol. 2016;75: 1162-70.e3.

27. Ständer S, Luger T, Cappelleri JC, et al. Validation of the Itch Severity Item as a measurement tool for pruritus in patients with psoriasis: results from a phase 3 tofacitinib program. Acta Derm Venereol. 2018;98:340–5.

28. Mease P, Hall S, FitzGerald O, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. N Engl J Med. 2017;377:1537–50.

29. Gladman D, Rigby W, Azevedo VF, et al. Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors. N Engl J Med. 2017;377: 1525–36.

30. Nash P, Coates LC, Fleishaker D, et al. Safety and efficacy of tofacitinib up to 48 months in patients with active psoriatic arthritis: final analysis of the OPAL Balance long-term extension study. Lancet Rheumatol. 2021;3:E270–83.

31. 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.

32. de Vlam K, Ogdie A, Bushmakin AG, et al. Median time to pain improvement and the impact of baseline pain severity on pain response in patients with psoriatic arthritis treated with tofacitinib. RMD Open. 2021;7: e001609.

33. 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.

34. Cappelleri JC, Zou KH, Bushmakin AG, Alvir JMJ, Alemayehu D, Symonds T. Patient-reported outcomes: measurement, implementation and interpretation. Boca Raton, FL: Chapman & Hall/CRC Press; 2013.

35. Ogdie A, de Vlam K, McInnes IB, et al. Efficacy of tofacitinib in reducing pain in patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. RMD Open. 2020;6: e001042.

36. Crispino N, Ciccia F. JAK/STAT pathway and nociceptive cytokine signalling in rheumatoid arthritis and psoriatic arthritis. Clin Exp Rheumatol. 2021;39:668–75.

37. Salaffi F, Giacobazzi G, Di Carlo M. Chronic pain in inflammatory arthritis: mechanisms, metrology, and emerging targets—a focus on the JAK-STAT pathway. Pain Res Manage. 2018;2018:8564215.

38. Krueger J, Clark JD, Suárez-Fariñas M, et al. Tofacitinib attenuates pathologic immune pathways in patients with psoriasis: a randomized phase 2 study. J Allergy Clin Immunol. 2016;137:1079–90.

39. Smith JA, Colbert RA. Review: the interleukin-23/interleukin-17 axis in spondyloarthritis pathogenesis: Th17 and beyond. Arthritis Rheumatol. 2014;66:231–41.

40. Sherlock JP, Joyce-Shaikh B, Turner SP, et al. IL-23 induces spondyloarthropathy by acting on ROR-γt+ CD3+CD4-CD8- entheseal resident T cells. Nat Med. 2012;18:1069–76.

41. Bautista-Herrera LA, De la Cruz-Mosso U, Román-Fernández IV, et al. A potential inflammatory role of IL-31 in psoriatic arthritis: a correlation with Th17 cytokine profile. Int J Immunopathol Pharmacol. 2020;34:2058738420907186.

42. Veale DJ, McGonagle D, McInnes IB, et al. The rationale for Janus kinase inhibitors for the treatment of spondyloarthritis. Rheumatology (Oxford). 2018;58:197–205.

43. Nattkemper LA, Tey HL, Valdes-Rodriguez R, et al. The genetics of chronic itch: gene expression in the skin of patients with atopic dermatitis and psoriasis with severe itch. J Invest Dermatol. 2018;138: 1311–7.

44. Liu T, Ji RR. New insights into the mechanisms of itch: are pain and itch controlled by distinct mechanisms? Pflugers Arch. 2013;465:1671–85.

45. Zhang X, He Y. The role of nociceptive neurons in the pathogenesis of psoriasis. Front Immunol. 2020;11:1984.

46. Baumbach P, Weiss T, Giermann C, Cubillos S, Meissner W, Norgauer J. Standardized quantitative sensory testing in patients with psoriasis vulgaris: evidence for altered large and small fibre functioning. J Eur Acad Dermatol Venereol. 2016;30: e137–40.

47. Yosipovitch G, Chan YH, Tay YK, Goh CL. Thermosensory abnormalities and blood flow dysfunction in psoriatic skin. Br J Dermatol. 2003;149: 492–7.

48. Riol-Blanco L, Ordovas-Montanes J, Perro M, et al. Nociceptive sensory neurons drive interleukin-23-mediated psoriasiform skin inflammation. Nature. 2014;510:157–61.

49. Fang D, Kong L, Cai J, et al. Interleukin-6-mediated functional upregulation of TRPV1 receptors in dorsal root ganglion neurons through the activation of JAK/PI3K signaling pathway: roles in the development of bone cancer pain in a rat model. Pain. 2015;156:1124–44.

50. Donnerer J, Liebmann I. The NK1 receptor antagonist SR140333 inhibits capsaicin-induced ERK phosphorylation in sensory neurons. Pharmacology. 2006;77:144–9.

51. Kilic G, Kilic E, Nas K, Kamanli A, Tekeoglu I. Residual symptoms and disease burden among patients with psoriatic arthritis: is a new disease activity index required? Rheumatol Int. 2019;39:73–81.

52. Husted JA, Tom BD, Farewell VT, Gladman DD. Longitudinal study of the bidirectional association between pain and depressive symptoms in patients with psoriatic arthritis. Arthritis Care Res (Hoboken). 2012;64:758–65.