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Identifying mediators of pain reduction in patients with psoriatic arthritis treated with tofacitinib: role of inflammation associated with peripheral arthritis, enthesitis and skin disease

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Background:

Treatment effect on pain is a priority for patients (pts) with psoriatic arthritis (PsA) and physicians. As pain is multidimensional, there is growing interest to understand the mechanisms of pain relief during treatment. Tofacitinib is an oral Janus kinase inhibitor for the treatment of PsA. Previous analyses showed that the effect of tofacitinib on pain in pts with PsA was partially mediated through improvement of inflammation as assessed by C-reactive protein (CRP) and Swollen Joint Count (SJC). Additional potential inflammation-associated mediators that might contribute to tofacitinib's effect on pain include enthesitis and skin disease.

Objectives:

To describe the interrelationship between pain, tofacitinib treatment and potential inflammatory-associated outcomes, using mediation modelling.

Methods:

Data from two Phase 3 studies (OPAL Broaden [NCT01877668]; OPAL Beyond [NCT01882439]) of pts with active PsA treated with tofacitinib 5 mg twice daily (BID) or placebo were used; pts were tumour necrosis factor inhibitor (TNFi)-naïve or had previous inadequate response to ≥1 TNFi. All pts were treated continuously with a single conventional synthetic DMARD. Analyses were completed using pooled and individual study data at Months 1 and 3 (using mean scores across visits). Mediation modelling seeks to explain mechanisms underlying observed relationships between independent and dependent variables via other variables (mediators). This initial model included: treatment as the independent (explanatory) binary variable (tofacitinib 5 mg BID vs placebo); pain, measured by Patient's Assessment of Arthritis Pain (VAS, 0–100 mm), as the dependent (outcome) variable; mediators were: pt-reported Itch Severity Index (ISI); CRP; SJC; Psoriasis Area and Severity Index (PASI); and enthesitis, measured by Leeds Enthesitis Index (LEI) or Spondyloarthritis Research Consortium of Canada Enthesitis Index (SPARCC). The final model was revised based on results of the initial model.

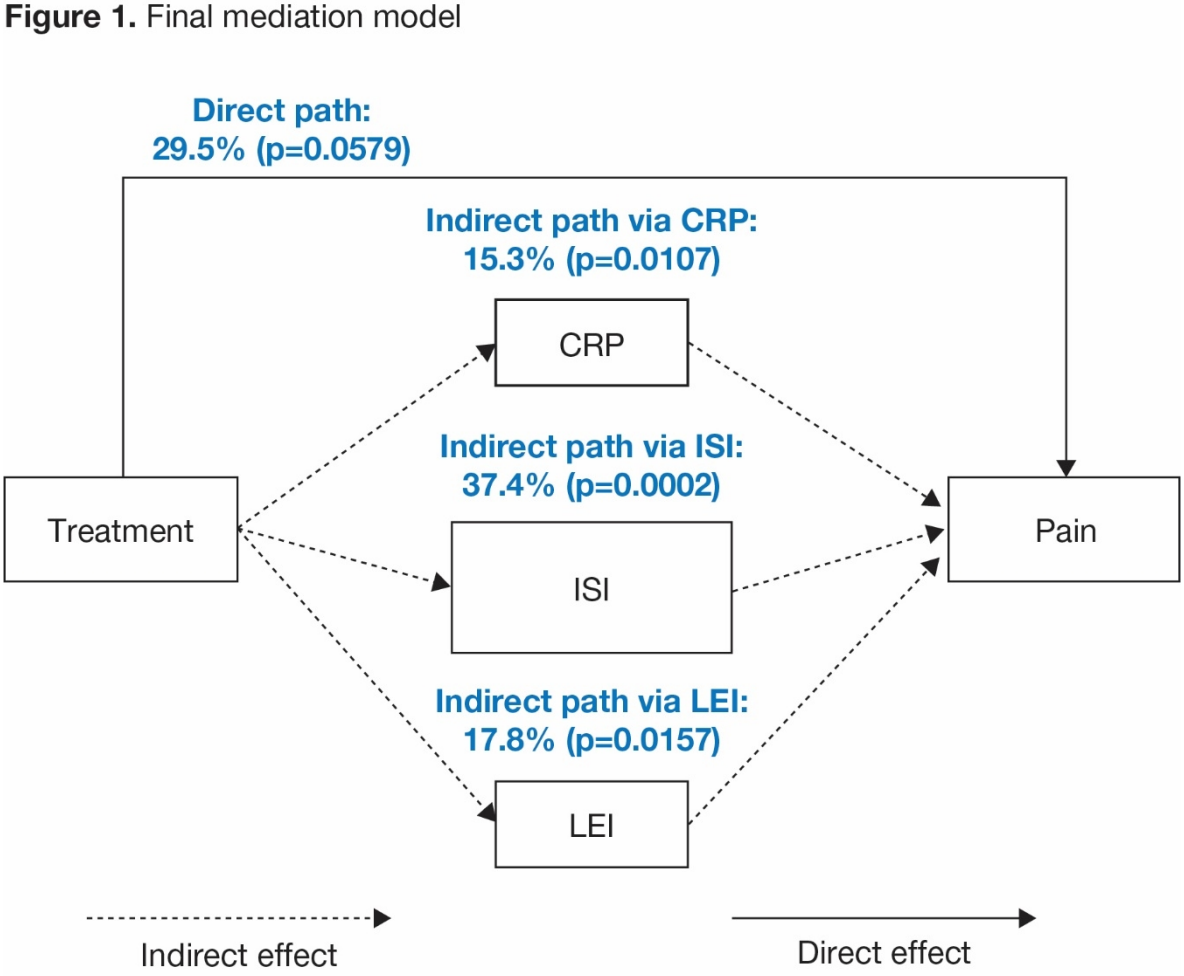
Results:

The initial model (N=329; pooled data) showed that tofacitinib treatment affects pain mainly indirectly via ISI, CRP, SJC, PASI and enthesitis (LEI), with 16.0% (p=0.53) attributable to the direct effect. The indirect effect via SJC (<1%) was not significant (p=0.99); the indirect effect via PASI was contradictory (-14.4%, p=0.10). The final model (Figure 1) excluded SJC and PASI. Analysis of the final model (N=468; pooled data) 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, LEI and CRP mediated 37.4% (p=0.0002), 17.8% (p=0.0157) and 15.3% (p=0.0107) of the tofacitinib treatment effect on pain, respectively. Results for individual studies were consistent with pooled data, as were those when enthesitis was represented by SPARCC in the model.

Conclusion:

The majority of tofacitinib treatment effect on pain in pts with PsA is collectively mediated by itch, enthesitis and CRP, with itch being the main mediator of treatment effect (~37%), using mediation modelling analyses.

Figure 1. Final mediation model



Treatment is represented by a binary variable (tofacitinib 5 mg BID vs placebo); pain was measured by Patient's Assessment of Arthritis Pain (VAS, 0–100 mm); inflammation was measured by CRP.

BID, twice daily; CRP, C-reactive protein; ISI, Itch Severity Index; LEI, Leed Enthesitis Index; VAS, Visual Analogue Scale

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