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Understanding mediators of pain reduction in psoriatic arthritis patients treated with tofacitinib: role of inflammation

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Background: Pain is a priority for patients (pts) with psoriatic arthritis (PsA) and physicians. Tofacitinib is an oral Janus kinase inhibitor for the treatment of PsA. As pain is a multidimensional phenomenon, there is growing interest in understanding mechanisms of pain relief during treatment.

Objectives: To examine the potential role of inflammation in the effect of tofacitinib on pain in pts with PsA, using mediation modelling.

Methods: Data were from the Phase 3 OPAL Broaden (NCT01877668)¹ and OPAL Beyond (NCT01882439)² studies of pts with active PsA treated with tofacitinib 5 mg twice daily (BID) or placebo; pts were tumour necrosis factor inhibitor (TNFi)-naïve or had previous inadequate response (IR) to ≥ 1 TNFi. All pts continued on a stable dose of a single conventional synthetic DMARD. Analyses used pooled and individual trial data (mean scores from Months 1, 2 and 3). Mediation modelling seeks to identify/explain

mechanisms underlying an observed relationship between an independent variable and a dependent variable via other explanatory variables (mediators). In this model, pain (reported by pts on a 100 mm visual analogue scale) was the designated dependent variable, treatment (tofacitinib 5 mg BID vs placebo) was the independent variable, and inflammation, measured by swollen joint count (SJC) and C-reactive protein (CRP), was a mediator. The primary model designated the treatment effect on pain mediated via CRP/SJC changes as an **indirect effect** and the treatment effect not attributable to CRP/SJC as a **direct effect**. Further analyses by population (TNFi-naïve vs TNFi IR pts) were performed. Models were re-specified based on initial model results; model invariance among pt populations was assessed.

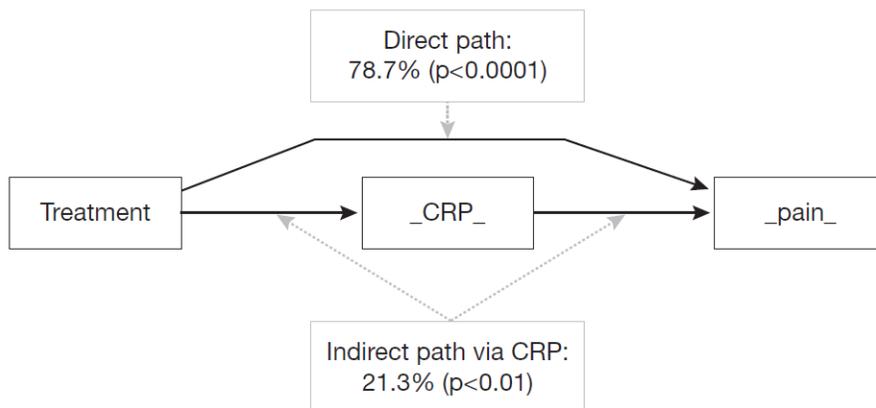
Results: In the pooled analysis (N=469), 25.9% ($p<0.01$) of the treatment effect of tofacitinib on pain was mediated by inflammation as assessed by CRP/SJC (indirect effect), of which changes via CRP and SJC were 17.8% ($p<0.01$) and 8.1% ($p>0.05$), respectively. The treatment effect on pain not attributable to CRP/SJC (direct effect) was 74.1% ($p<0.0001$). In TNFi-naïve and TNFi-IR pts, indirect effects via SJC were not statistically significant. In the re-specified model with CRP as sole mediator, the indirect effect was 21.3% for pooled data ($p<0.01$; Figure a) and 36.1% ($p<0.05$) and 16.7% ($p<0.05$) for TNFi-naïve and TNFi-IR pts, respectively (Figures b, c); the 19.4% difference between TNFi-naïve vs TNFi-IR pts was not statistically significant.

Conclusions: While inflammation, as assessed by CRP/SJC, was a significant mediator of the overall treatment effect on pain tofacitinib-treated pts with PsA, the majority of the treatment effect was not attributable to CRP/SJC changes. When mediators were assessed individually, only CRP, was a significant mediator in the pooled analysis. In the re-specified model, CRP-mediated effects differed in TNFi-naïve vs TNFi-IR pts, but this was not statistically significant. These results suggest that CRP/SJC-associated inflammation only partially explains pain in PsA; other potential mediators need to be identified to better understand the treatment effect of tofacitinib on pain.

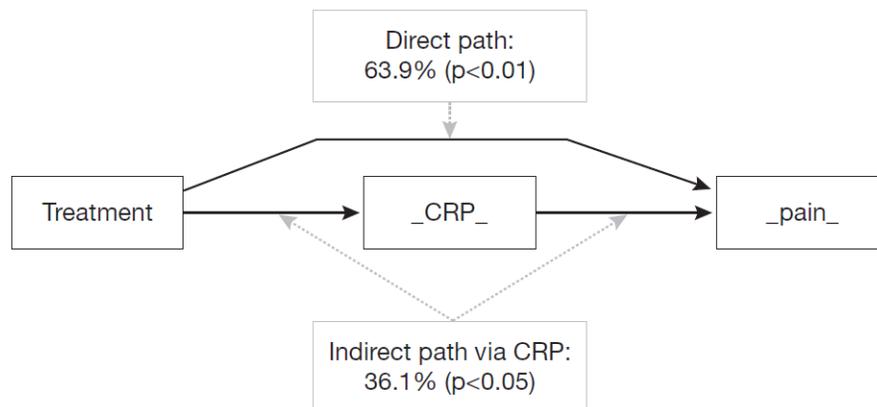
References: 1. Mease P et al. N Engl J Med 2017;377:1537-50. 2. Gladman D et al. N Engl J Med 2017;377:1525-36.

Figure. Mediation effects: A. Overall treatment effects on pain, and indirect effect of CRP; B. Indirect effects of CRP in OPAL Broaden; C, Indirect effects of CRP in Opal Beyond

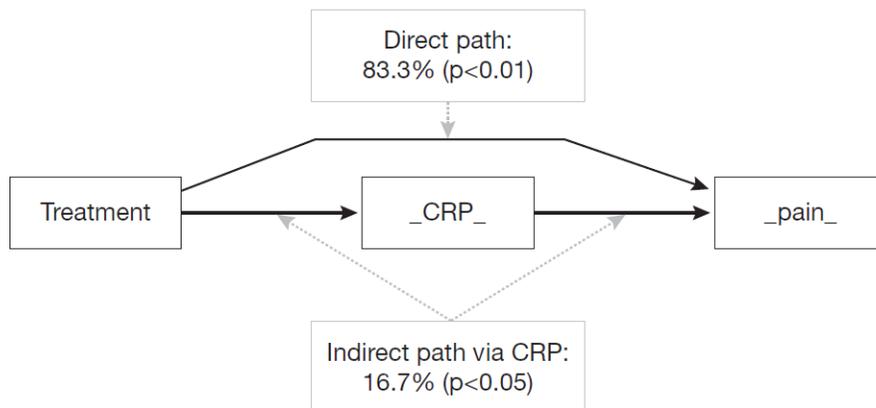
A. Pooled data



B. OPAL Broaden



C. OPAL Beyond



Pain was measured by Pt's Assessment of Arthritis Pain (0–100mm); The mediation model included mean data for pain and CRP from M1, M2 and M3; "treatment" was represented in the model by a binary variable ("tofacitinib 5 mg BID"=1; "PBO"=0) BID, twice daily; CRP, C-reactive protein; M, month; PBO, placebo; pt, patient

