Examining the Relationships Among Abrocitinib Treatment, Itch, Skin Pain, and Dermatology-specific Quality of Life in Patients With Atopic Dermatitis: A Mediation Modeling Analysis

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Background: Atopic dermatitis (AD) is a chronic inflammatory skin disease associated with itch, eczematous lesions, and impaired quality of life (QoL). Although the frequency of skin pain in AD is often underestimated, it is associated with a substantial health burden, similar to itch, and is known to contribute to sleep disruption and mood disturbance. Abrocitinib is an oral, once-daily, selective Janus kinase-1 inhibitor approved for the treatment of moderate-to-severe AD. In the phase 3 clinical trials JADE MONO-1 (NCT03349060) and JADE MONO-2 (NCT03575871), abrocitinib demonstrated rapid relief from itch and skin pain, as well as meaningful improvements in QoL compared with placebo. The interrelationships among abrocitinib treatment and improvements in itch, skin pain, and QoL have not yet been investigated.

Objective: This mediation analysis aimed to characterize the effect of abrocitinib treatment via itch and skin pain on dermatology-specific QoL in patients with AD.

Methods: Data from JADE MONO-1 and JADE MONO-2 were pooled in this analysis. Adult patients with moderate-to-severe AD received abrocitinib (200 mg or 100 mg) as monotherapy or placebo for 12 weeks. Three separate models were evaluated whereby QoL was assessed using the Dermatology Life Quality Index (DLQI) score, and itch and skin pain were assessed via the Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) items #1 (*How itchy was your skin over the past 24 hours?*) and #2 (*How painful was your skin over the past 24 hours?*), respectively. The cross-sectional mediation model (CSMM) was run separately at weeks 2, 4, 8, and 12 using all available data at each timepoint. The longitudinal mediation model (LMM), which does not assume independence among measurements of itch, skin pain, and DLQI at each timepoint, estimated relationships using all available data from all weeks simultaneously. Based on the results of the CSMM and LMM, a pseudo steady-state model, in which the relationship among variables was assumed to be the same across timepoints, was applied. Effects with $P<0.05$ were considered statistically significant.

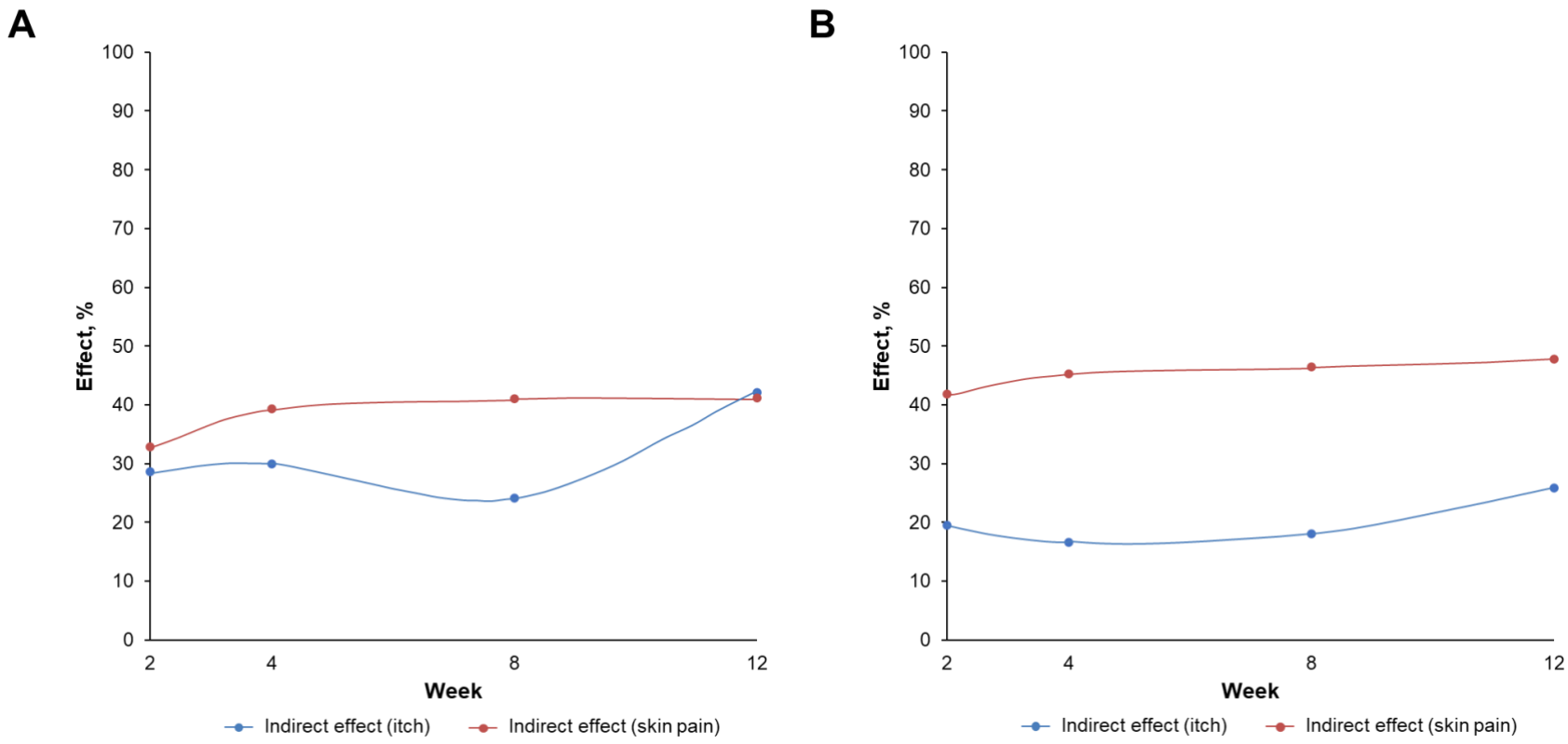
Results: In the CSMM, the indirect effect of abrocitinib on DLQI mediated via itch was considered approximately stable (24%–30%) for the first 8 weeks before increasing at week 12 (42%), while the indirect effect mediated via skin pain was considered approximately stable from week 2 to week 12 (33%–41%; **Figure 1A**). In the LMM, the indirect effect of abrocitinib treatment on DLQI mediated via both itch and skin pain was considered approximately stable from week 2 to week 12 (17%–26% and 42%–48%, respectively; **Figure 1B**). The cross-sectional and longitudinal models were generally consistent and indicated a pseudo steady-state period between weeks 2 and 12. Using the pseudo steady-state model, the direct effect of abrocitinib on DLQI was estimated to be 34.8% ($P<0.0001$), and the indirect effects mediated

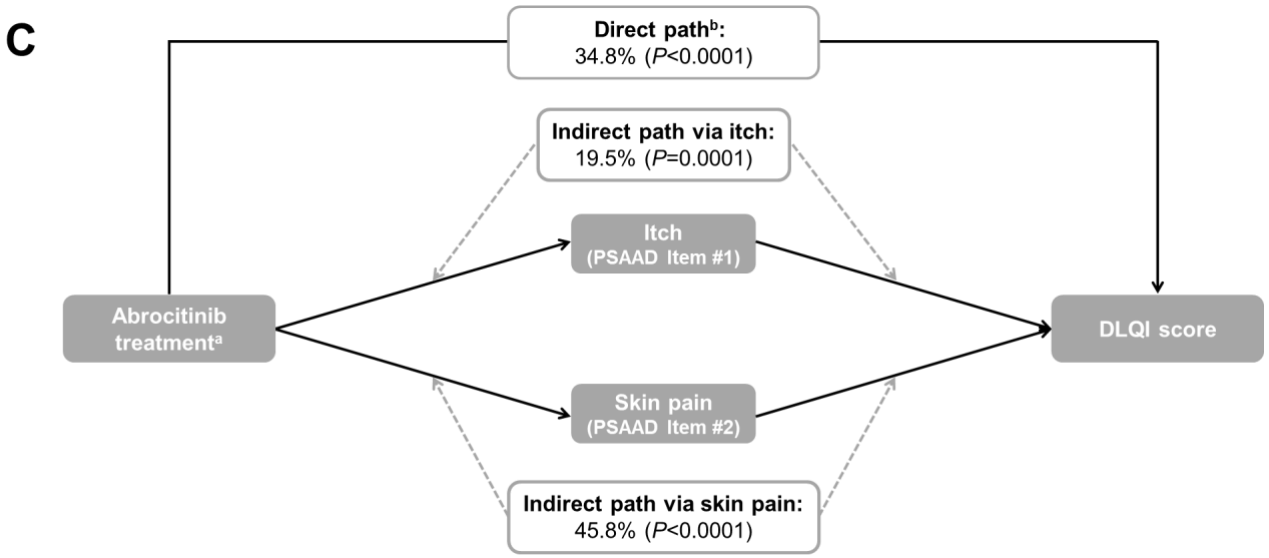
via itch and skin pain were estimated to be 19.5% and 45.8%, respectively ($P \leq 0.0001$ for both; **Figure 1C**).

Conclusions: Improvements in dermatology-specific QoL with abrocitinib are mostly mediated indirectly via reduction in skin pain and less so by relief of itch. These findings warrant further research to examine to what extent patients consider itch and skin pain as separate concepts in terms of their impact on dermatology-specific QoL.

Keywords: abrocitinib, atopic dermatitis, skin pain, itch, quality of life**.**

Figure 1. Direct and indirect effects of abrocitinib treatment on dermatology-specific quality of life in patients with atopic dermatitis as estimated via a (**A**) cross-sectional model, (**B**) longitudinal model, and (**C**) pseudo steady-state longitudinal model





DLQI, Dermatology Life Quality Index; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis.

[a]Abrocitinib treatment is a binary variable representing abrocitinib versus placebo.

[b]Direct path represents the effects of other factors not included in the model.

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