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Topical pan-JAK inhibition with delgocitinib restores the molecular signature of lesional skin in patients with Chronic Hand Eczema

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Introduction & Objectives: Chronic Hand Eczema (CHE) is a multifactorial, inflammatory skin disease characterized by several clinical subtypes and association with innate immune and T helper (Th)1/Th2 /Th17 inflammation. Delgocitinib, a pan-Janus kinase (JAK) inhibitor, blocks JAK-mediated signalling of inflammatory cytokines that play a key role in CHE pathogenesis. In this analysis, we investigated (1) the molecular endotype underlying CHE and (2) to what extent the topical application of delgocitinib ointment reduced local inflammation and restored skin barrier function.

Materials & Methods: Seventy-two biopsy samples from 41 patients with CHE from the Phase 2a trial (NCT02664805) were collected: 38 from baseline and 34 from end of treatment (EoT). Thirty-one patients (delgocitinib ointment: n=20; ointment vehicle: n=11) had paired samples from both baseline and EoT. RNA was extracted and global gene expression was profiled by microarray analysis. A pairwise comparison of biomarker expression was made between severe, moderate, and mild CHE at baseline. Severe and mild CHE were compared to assess the regulation of the most relevant inflammatory pathways, including the Th1/Th17 and JAK pathways. A comparison between baseline and EoT was made for both the delgocitinib and vehicle groups. The gene set analysis was conducted on the Gene Ontology (GO) biological processes, and annotated gene sets and pathways collected in Reactome and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases.

Results: Gene expression largely differed between patients with severe and mild CHE, including the downregulation of genes associated with maintaining skin barrier homeostasis in severe cases (e.g., *LORICRIN*, *FLG2*, and *SERPINA12*), and upregulation of genes involved in the Th1, Th17, Th22, and Th2 immune pathways. Delgocitinib treatment led to a significant normalization of the dysregulated genes in the Th1, Th17, Th22, (all $P<0.05$) and Th2, and JAK pathways ($P<0.01$). Furthermore, delgocitinib treatment normalized the expression of key skin barrier function and tissue integrity markers that were downregulated at baseline, including *FLG*, *FLG2*, *AQP9*, *SCEL*, and *LORICRIN* ($P<0.001$); none were up- or down-regulated in samples from vehicle patients. Delgocitinib-treated patients demonstrated normalized GO biological processes in the gene set analysis, with epidermis development and keratinocyte differentiation being among the most significant.

Conclusion: Severe CHE was associated with a strong dysregulation of genes in various pathways involved in skin inflammation and barrier function. Delgocitinib normalized the inflammatory processes and restored skin barrier integrity in CHE by inhibiting JAK signalling pathways.