ATOPIC ECZEMA/DERMATITIS

INHIBITORY EFFECTS OF BARICITINIB ON A HUMAN SKIN MODEL OF ATOPIC DERMATITIS

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Introduction: Atopic dermatitis (AD) is a common inflammatory and pruritic skin disease characterized by complex cytokine signaling involving cross-talk between keratinocytes (KCs), neurons, immune cells, and inflammatory mediators. Baricitinib is a JAK1/JAK2 inhibitor in Phase 3 clinical development for AD.

Objective: We sought to decipher the role of JAK1/JAK2 signaling with baricitinib using a 3-dimensional (3D) model possessing AD-like pathology.

Materials and Methods: Human skin equivalents were processed by MatTek (Ashland, MA) using neonatal human skin KCs overlaid on a collagen matrix embedded with fibroblasts. Skin cultures raised to an air-liquid interface were maintained for 3 days either in medium alone, or medium containing a cytokine cocktail with interleukins (IL) that are elevated in lesional AD skin i.e., IL-4, IL-13, and IL-31. Skin cultures were treated with or without baricitinib (150 nM). Skin samples were processed for immunohistology and filaggrin expression, with RNA isolated and analyzed using microarrays.

Results: Treatment with this cytokine cocktail induced several histopathological alterations classically observed in eczematous lesions such as diminished granular cell layer and increased spongiosis accompanied by filaggrin immunostaining reduction. Gene expression analyses focusing on the epithelial differentiation complex (EDC) revealed similarities between the AD 3D model and lesional AD tissue. Adding baricitinib to the cytokine cocktail reduced the AD-like pathology induced in the skin model.

Conclusions: These data indicate that it is possible to create a physiologically-relevant 3D model resembling AD pathology using a combination of different cytokines. This 3D model provides an opportunity to further investigate the potential role of different cytokines and inflammatory pathways in AD. These data support that JAK1/JAK2 signaling contributes to the cytokine-induced pathology of AD, with baricitinib treatment reducing pathological alterations, and provides a path forward for further understanding the mechanism of action of baricitinib in AD.