AUTOIMMUNE CONNECTIVE TISSUE DISEASES

CLINICAL RESPONSE TO JAK INHIBITION IN PATIENTS WITH FAMILIAL CHILBLAIN LUPUS AND TREX1 MUTATION

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Introduction: Familial chilblain lupus (FCL) is a monogenic autosomal dominant form of cutaneous lupus erythematosus based on mutations in three prime repair exonuclease 1 (TREX1). FCL presents in early childhood with cold-induced painful erythematous infiltrates leading to mutilation. It is associated with variable systemic involvement and treatment is currently insufficient.
The cytosolic DNase TREX1 safeguards the cell against innate immune activation. In TREX1 deficient cells, self DNA accumulates in the cytosol and stimulates the type I-IFN pathway. Inappropriate chronic type I-IFN activation can break immune tolerance and promote autoimmunity. Consequently, patients with FCL exhibit constitutive upregulation of IFN-stimulated genes (ISGs) in blood and skin. Type I-IFNs signal via the IFN-α/β receptor and Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway.

Objective: To evaluate the clinical response to the JAK inhibitor baricitinib in FCL and assess the effect of cold on patient fibroblasts.

Materials and Methods: In 3 adult patients with FCL we initiated treatment with baricitinib 4mg daily for 3 months. ISG expression was analysed by PCR. Patient derived fibroblasts were investigated for cold induced stress response in vitro.

Result: All 3 patients showed a significant reduction of cutaneous lupus lesions measured by revised cutaneous lupus area and severity index. We observed a decrease of the systemic type I-IFN signature in blood. One patient had complete pain relief and in two patients pain associated with joint inflammation was partially reduced. No severe adverse reactions were reported.
Exposure of patient fibroblast to cold induced a stress response, enhanced senescence and induction of ISG.

Conclusion: Our findings demonstrate the therapeutic efficacy of JAK inhibition in FCL and give mechanistic insight into the process of disease exacerbation by cold in TREX1-deficient cells. This may be relevant for implicating JAK inhibition as a therapeutic option also in multifactorial lupus erythematosus and other interferonopathies.