INTERLEUKIN-31 IS ELEVATED IN DERMAL INTERSTITIAL FLUID IN SYSTEMIC SCLEROSIS AND MAY BE A KEY MEDIATOR OF ITCH IN BOTH DIFFUSE AND LIMITED CUTANEOUS DISEASE

Sara Zafar, Bahja A. Abdi, Fiona Xing, Oseme Etomi, Charlotte Wong, David Abraham, Christopher P. Denton and Richard J. Stratton

Department of Inflammation, Centre for Rheumatology and Connective Tissue Diseases, Royal Free Hospital, London, UK

Background: Severe, intractable pruritus is a debilitating symptom in approximately 40% of SSc cases. It has been particularly associated with severe diffuse skin disease and resolution often coincides with clinical improvement in cutaneous sclerosis. Resistance of itch to treatment with classical anti-histamine based-therapy makes it especially challenging. The pathophysiology of itch is complex, involving several immuno-neurological factors. One novel cytokine, IL-31, produced by dermal mast cells and most notably, differentiated activated CD4+ T helper 2 cells, has been implicated in mediating allergy and atopy. Studies have demonstrated elevated serum IL-31 and upregulated IL-31 mRNA, in patients with severe itch due to chronic dermatoses such as atopic eczema, allergic contact dermatitis and nodular prurigo. In some cases, IL-31 levels correlated with disease activity. Studies of transgenic mice have suggested IL-31 induces severe pruritus and serum levels correlate with scratching behaviour. In this study, we explore the role of IL-31 in the pathophysiology of itch in patients with SSc and consider the cytokine a novel target for therapeutic modulation.

Methods: IL-31 levels in dermal blister-fluid and serum samples were measured using ELISAs in a cohort of SSc cases and healthy controls. SSc cases with pruritus were asked to complete the standardized 5D-Pruritus questionnaire to enable quantitative analysis of itch severity. RT-PCR was employed to determine IL-31 and IL-31 receptor expression, using messenger RNA extracted from dermal keratinocytes. Flow cytometry will be performed to analyse intracellular IL-31 expression and clinical correlation will be undertaken, to evaluate the relationship between itch severity, disease characteristics and IL-31 levels.

Results: IL-31 expression was significantly increased in the dermal blister-fluid of some of the 26 SSc cases, with a mean IL-31 concentration 125.7 pg/ml vs 2.3 pg/ml in the 15 healthy controls (Z = -2.54, P = 0.006). Subgroup analysis revealed that the 12 limited cutaneous SSc cases in this study had a mean interstitial fluid IL-31 of 80.1 pg/ml, compared with a mean of 164.8 pg/ml in the 14 diffuse cases (P > 0.05). In addition, 90 serum samples were analysed for IL-31 concentration; a mean of 196 pg/ml was found in the 27 healthy controls, compared with 1914 pg/ml in the 63 SSc patient samples, with a trend to statistical significance (Z = -1.64, P = 0.05). Preliminary data have demonstrated a 3.7-fold increase in IL-31 receptor gene expression between SSc and control RNA.

Conclusion: Together, these results suggest that IL-31 may be increased in SSc and that this difference is especially seen in dermal interstitial fluid. This makes IL-31 a key candidate mediator for the intractable itch that may be a hallmark of active SSc skin disease and may represent a novel therapeutic target. Furthermore, the IL-31 axis may play a role in other aspects of the pathophysiology of SSc; thus, further evaluation is warranted.

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