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Differentially expressed plasma proteins in pityriasis rubra pilaris patients treated with ixekizumab

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Abstract

Pityriasis Rubra Pilaris (PRP) is a rare and debilitating cutaneous disease characterized by widespread red scaly plaques, follicular papules, and palmoplantar keratoderma. The pathogenesis of PRP is poorly understood, although overexpression of Th17 cytokines have been reported suggesting an inflammatory pathogenesis that may share features with psoriasis. In this study, we used OLINK proximity extension assay technology to quantitate 92 plasma inflammatory proteins of 11 PRP patients treated with ixekizumab (NCT03485976). Samples were obtained at baseline (week-0) and the final study visit (week-24). Comparisons of plasma protein concentrations were made between pretreatment and posttreatment samples and between responders (as defined by a ≥50% improvement in Psoriasis Area and Severity Index [PASI50]) and nonresponders. P-values were adjusted for multiple hypotheses. Of the 92 proteins analyzed, we identified a paradoxical 5.7-fold upregulation of IL-17A at week-24 compared to baseline ($p<0.000001$), in contrast to previous reports of decreased plasma IL-17A gene expression in patients treated with ixekizumab for psoriasis. When stratified by treatment response status, responders had significantly lower levels of IL-17 and TNF family cytokines, including IL-17C ($p<0.0001$) and TNF ($p=0.001$), at week-24 compared to nonresponders, suggesting that additional inhibition of the Th17 axis may be required to treat recalcitrant cases of PRP. This observation was supported clinically by a nonresponder patient who had treatment success with an increased dose of ixekizumab after trial completion. To our knowledge, this is the first quantitative protein analysis of PRP. These findings support prior studies implicating dysregulation of the Th17 axis in PRP and may help elucidate relevant pathways to target and better treat PRP. Further research is warranted to compare samples to a control population, and to compare these systemic biomarkers to local changes in skin samples.