

## Skin morphological analysis upon treatment with anti-TNF-alpha agents in psoriatic patients

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Psoriasis is the most common immune-mediated skin disease worldwide, with an estimated incidence of about 2%. It is characterized by erythematous scaly plaques and its pathogenesis is mostly due to an interplay among epidermal cells, immunocompetent cells, and pro-inflammatory cytokines. Previous studies on psoriatic skin demonstrated delayed terminal differentiation, keratinocyte hyperproliferation, and abnormal occludin expression in tight junctions. However, evidences about desmosomal cadherin distribution in psoriatic patients are not available so far, and only scattered studies have been carried out on adherens junctions. In psoriasis, Tumor Necrosis Factor- alpha (TNF-alpha) plays a central role, strongly supporting the treatment with anti-TNF-alpha agents, but the effects of these agents on epidermal intercellular adhesion, terminal differentiation, and proliferation have still to be elucidated.

In this preliminary study, we investigated by immunofluorescence the expression of transmembrane proteins in tight junctions (occludin), adherens junctions (E-cadherin), and desmosomes (desmocollin-1 and desmoglein-1) in normal (N=5) and psoriatic skin before/after treatment with anti-TNF-alpha agents (N=5). Differentiation biomarkers (keratin-10, keratin-14, and involucrin) and epithelial proliferation were also evaluated.

In psoriatic epidermis occludin, keratin-14, and involucrin were expressed also in the spinous layer, differently from controls. Desmoglein-1, desmocollin-1, E-cadherin, and keratin-10 localizations were comparable in psoriatic and healthy subjects. Moreover, in all considered patients the hyperproliferative condition was accompanied by an unusual suprabasal distribution of replicating keratinocytes. Interestingly, the distribution pattern of all considered biomarkers of intercellular adhesion and terminal differentiation was reverted to the physiological condition upon treatment with anti-TNF-alpha agents. What's more, the proliferative rate registered in anti-TNF-alpha treated patients was reduced and similar to controls, even though scattered suprabasal dividing cells were still present.

Our results highlight that anti-TNF-alpha biologicals, next to their proven inhibitory action on the cytokinic pathway, are effective in restoring an efficient junctional apparatus, a more differentiated phenotype, and the typical proliferation rate in the epidermis of psoriatic patients.

**Keywords:** desmosomes, tight junctions, adherens junctions, proliferation, terminal differentiation, keratinocytes