Secukinumab Treatment Rapidly Leads to Positive Proteomic and Transcriptional Changes in Psoriatic Skin

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Introduction & Objectives

Secukinumab is a fully human antibody that targets IL-17A for the treatment of inflammatory diseases, including psoriasis. To gain insight into its mechanism of action in the psoriatic target tissue, the skin, we investigated early changes in the transcriptional and proteomic profiles in the epidermis (via tape strips), dermis (interstitial fluid obtained by dermal open flow microperfusion [dOFM]), and epidermis/dermis (via biopsies) in subjects with psoriasis after a single subcutaneous (s.c.) dose of secukinumab 300mg.

Materials & Methods

This single-center, open-label exploratory study was conducted using samples obtained from 8 subjects with moderate-to-severe psoriasis plaques who received a single s.c. dose of secukinumab on Day 1. Transcriptional data from lesional biopsies at Baseline and Day 8 were obtained using Affymetrix gene expression arrays, Nanostring nCounter custom code sets, and qPCR. Using Aushon BioSystems' multiplex biomarker platform, changes in 170 proteins were evaluated in lesional skin using tape strips and lesional and non-lesional interstitial fluid at Baseline and on Day 8 after dosing with secukinumab.

Results

At 8 days after a single s.c. dose of secukinumab, significant reductions were observed in mRNA and/or protein levels of inflammatory cytokines and chemokines (e.g., IL-1b, IL-17A, IL-17C, CXCL1, IL-8, IL-23/p19, IL-19, IL-36 family members) as well as mediators affecting keratinocyte proliferation (e.g., amphiregulin, epiregulin, IL-22). Interestingly, the expression of several genes associated with skin integrity (e.g., MMPs) and epidermal differentiation (e.g., filaggrin, desmocollin) was also changed towards normal levels at this early time point, indicating that healing of the psoriatic skin was already ongoing at the molecular level.

Conclusions

To the best of our knowledge, this is the first study in which changes at the protein level were investigated in psoriatic skin after anti–IL-17A therapy. In combination with novel sampling approaches (e.g., dOFM) and by combining the protein data with mRNA analysis, we were able to see that key molecular factors and processes implicated in psoriasis pathology were already positively impacted by 8 days after a single dose of secukinumab. The results further strengthen the central role of IL-17A in the pathogenesis of psoriasis and shed more light on the rapid changes observed with novel anti–IL-17A therapies.