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

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Background and Objectives

Secukinumab, a fully human monoclonal antibody that selectively targets IL-17A, has demonstrated rapid and significant efficacy in phase 3 trials, with approximately 70% of subjects in moderate-to-severe psoriasis achieving a PASI 50 response within 16 weeks of initiation of treatment.3

The objective of this exploratory, single-center, open-label study (NCT01535132) was to further characterize the mechanism of action of secukinumab by investigating early proteomic and transcriptional changes in the skin of subjects with psoriasis following a single s.c. dose of secukinumab.

Early proteomic and transcriptional changes were measured in multiple layers of psoriatic skin

A single 300 mg s.c. dose of secukinumab was administered on Day 1. After baseline samples were obtained, 6 psoriasis subjects with severe moderate-to-severe psoriasis were randomized to placebo or to receive secukinumab 300 mg on Day 1. Skin biopsy samples were harvested on Day 8 and Day 15.

Skin biopsies, sampling the epidermis and dermis, were taken at baseline and approximately 70% of subjects with moderate-to-severe psoriasis achieving a PASI 50 response within 16 weeks of initiation of treatment.3

Gene expression changes in skin biopsies were analyzed by Nanostring nCounter technology. Commercial skin biopsies (Asterand) from healthy volunteers (n = 10) served as controls.

Results

Secukinumab rapidly affected gene expression of IL17A and other inflammatory cytokines and chemokines in psoriatic lesions

- A tendency towards reduced mRNA expression of IL17A and other IL-17 family members (e.g. IL17C) was observed within 7 days of a single s.c. dose of secukinumab
- Expression of cytokine genes that drive IL-17A production and the Th17 response (e.g. IL23A) also appeared to be affected by secukinumab treatment
- Reductions in mRNA levels of 10–15 family cytokines (e.g. IL36A), which, with IL-17A, jointly amplify inflammation were also observed
- mRNA expression of neutrophil-attracting chemokines (e.g. CXCL1 and CXCL2) was rapidly downregulated, indicating that attenuation of neutrophil influx into inflammatory psoriatic plaques may be an early effect of secukinumab treatment

Conclusions

Secukinumab led to rapid positive changes in the expression of genes associated with skin integrity and epidermal differentiation

- Secukinumab upregulated the mRNA expression of Flggin (FLG) and keratin (KRT), important epidermal barrier proteins that are downregulated in psoriatic skin.

- Secukinumab also induced positive transcriptional changes in a number of genes involved in epidermal differentiation, such as small proline rich proteins (SPRRs), late cornified envelope (LCE) genes and desmoscin (KRT2) which are dysregulated in psoriatic skin.

- Evidence for rapid enhancement of keratinocyte proliferation and integrity was observed in psoriatic skin treated with secukinumab.

- Keratin molecular factors and epidermal differentiation markers of psoriasis were positively impacted in psoriatic skin within 7 days of treatment with a single s.c. dose of secukinumab 300 mg

- Secukinumab affected the expression of a number of cornified envelope proteins and keratin genes that are dysregulated in psoriasis, such as EGF, FILAGGRIN, IL17A, IL23A, KRT6A, KRT16 and LCE1C.

- Protein levels of epidermal and epidermal keratinocytic differentiation markers were decreased in psoriasis skin within the first 7 days of secukinumab treatment, consistent with clinical findings from phase 3 trials, indicating that, by inhibiting IL-17A, secukinumab can induce rapid positive changes in the underlying pathophysiology of psoriasis as early as 1 week after treatment.