

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



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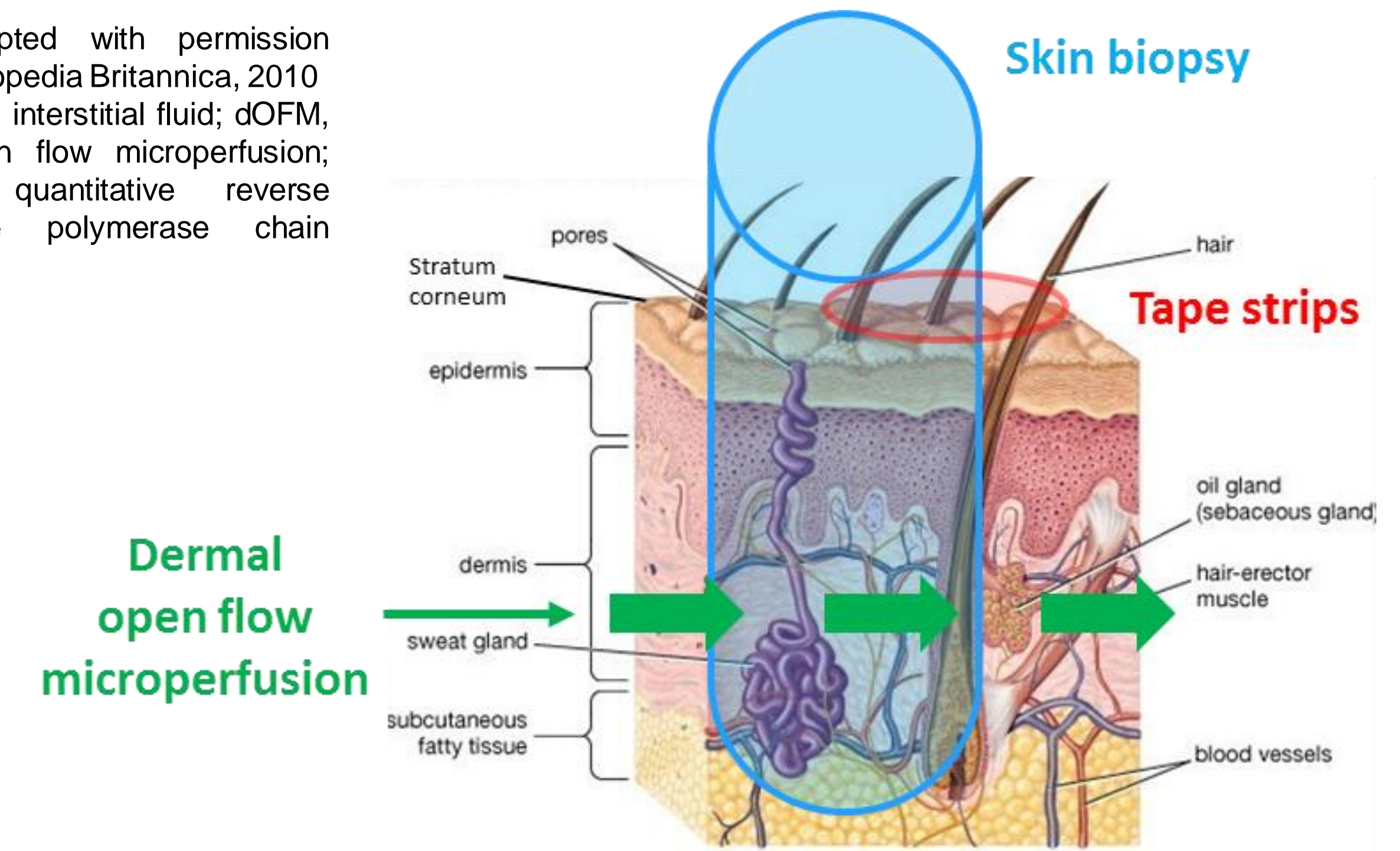
Background and objectives

- 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 with moderate-to-severe psoriasis achieving a PASI 90 response within 16 weeks of initiation of treatment¹
- Secukinumab treatment leads to a rapid onset of efficacy with a median time to 50% reduction in mean psoriasis area and severity index (PASI) score from baseline of 3 weeks with 300 mg versus 7 weeks with etanercept (P = 0.0001)¹
- The objective of this exploratory, single-center, open-label study (NCT01539213) 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 subcutaneous (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) to 8 psoriasis subjects with suitable moderate-to-severe target plaques
- The epidermis from lesional (psoriatic plaque) and non-lesional skin of subjects with psoriasis was sampled via tape strips at baseline (Day 1), Day 8 and Day 15
- Dermal open flow microperfusion (dOFM), a minimally invasive technique that has recently been validated as a method of sampling the dermal interstitial fluid (dISF)^{2,3}, was performed at baseline, Day 8 and Day 15 at lesional and non-lesional areas of skin from subjects with psoriasis
- Skin biopsies, sampling the epidermis and dermis, were taken at baseline and Day 8 from lesional skin of subjects with psoriasis
- Gene expression changes in skin biopsies were analyzed by Nanostring nCounter custom code sets and qRT-PCR. Commercial skin biopsies (Asterand) from healthy subjects (n = 10) served as controls
- Proteomic changes in tape strips and/or dISF were analyzed using Aushon Biosystems' multiplex biomarker platform

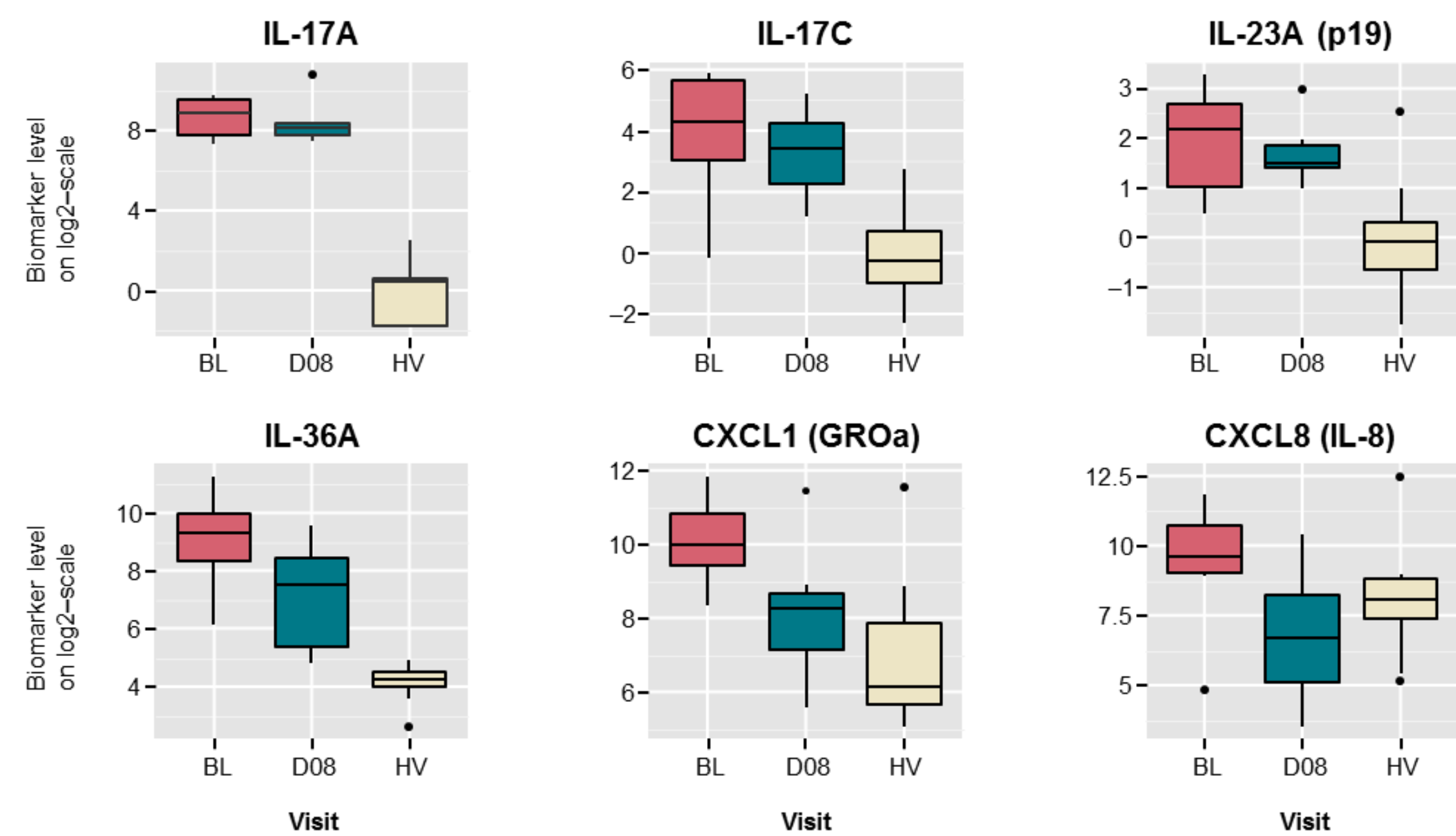
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dISF, dermal interstitial fluid; dOFM, dermal open flow microperfusion; qRT-PCR, quantitative reverse transcriptase polymerase chain reaction



RESULTS

Secukinumab rapidly affected IL-17A and other inflammatory cytokine and chemokine gene expression in psoriatic lesions

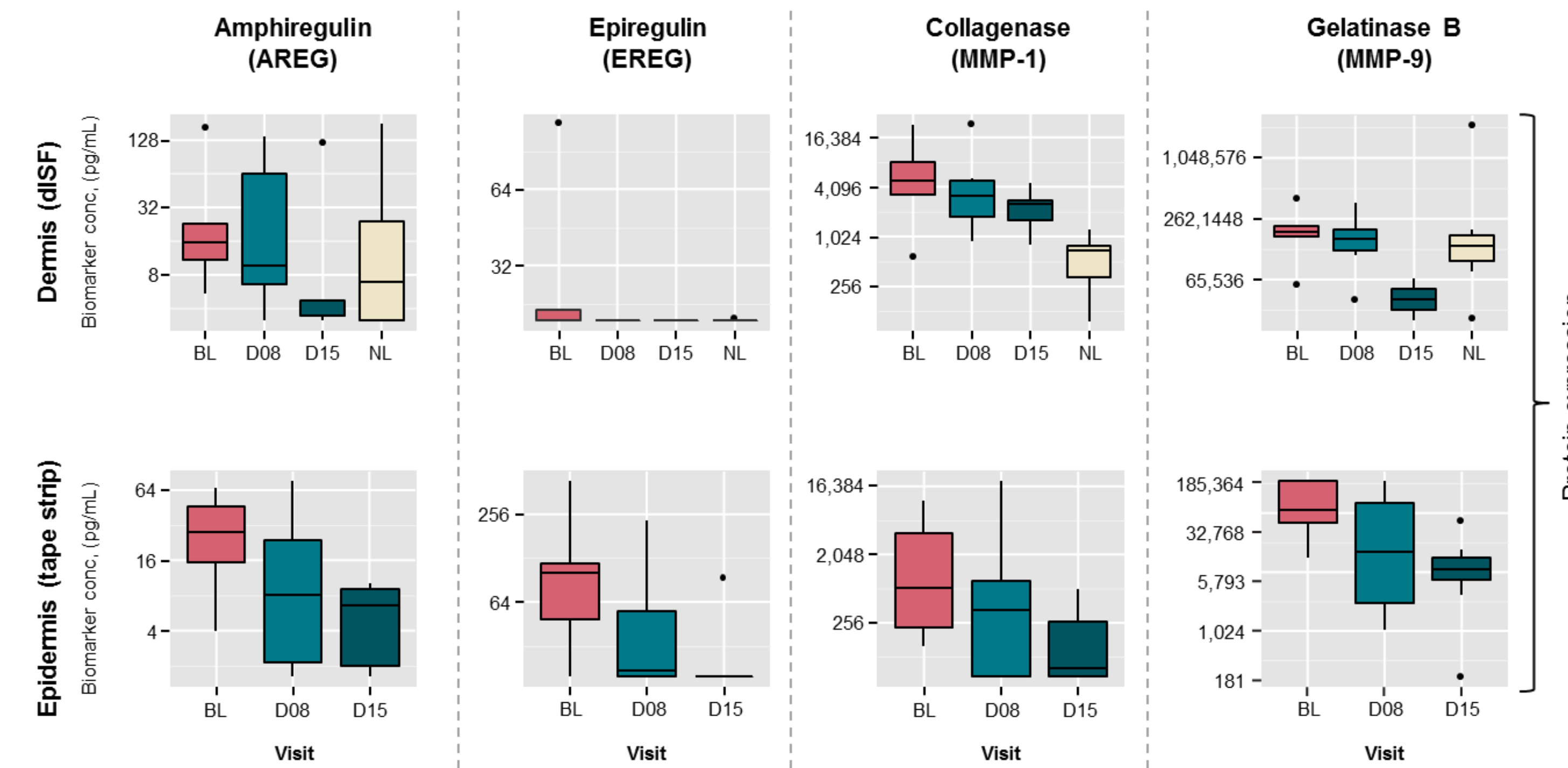
- There was already a tendency towards reduced mRNA expression of IL-17A and other IL-17 family members (e.g., IL-17C) within 7 days of a single s.c. dose of secukinumab
- Expression of cytokine genes that drive IL-17A production and Th17 responses (e.g., IL-23A) also appeared to be affected by secukinumab treatment
- Reductions in mRNA levels of IL-36 family cytokines (e.g., IL-36A), which jointly with IL-17A amplify inflammation,⁴ were also observed
- mRNA expression of neutrophil-attracting chemokines (e.g., CXCL1 and CXCL8) was rapidly downregulated, indicating that attenuation of neutrophil influx into inflammatory psoriatic plaques may be an early effect of secukinumab treatment



Data represent median (horizontal line), first and third quartiles (box) and range (vertical line). Outliers plotted as individual points. Quantitative values represent relative gene expression levels. Values for IL17A, IL17C and IL23A were scaled to respective mean expression level in HV
BL, baseline; CXCL, chemokine (C-X-C motif) ligand; D, day; HV, healthy volunteers.

Expression of proteins associated with keratinocyte proliferation and integrity was rapidly downregulated by secukinumab

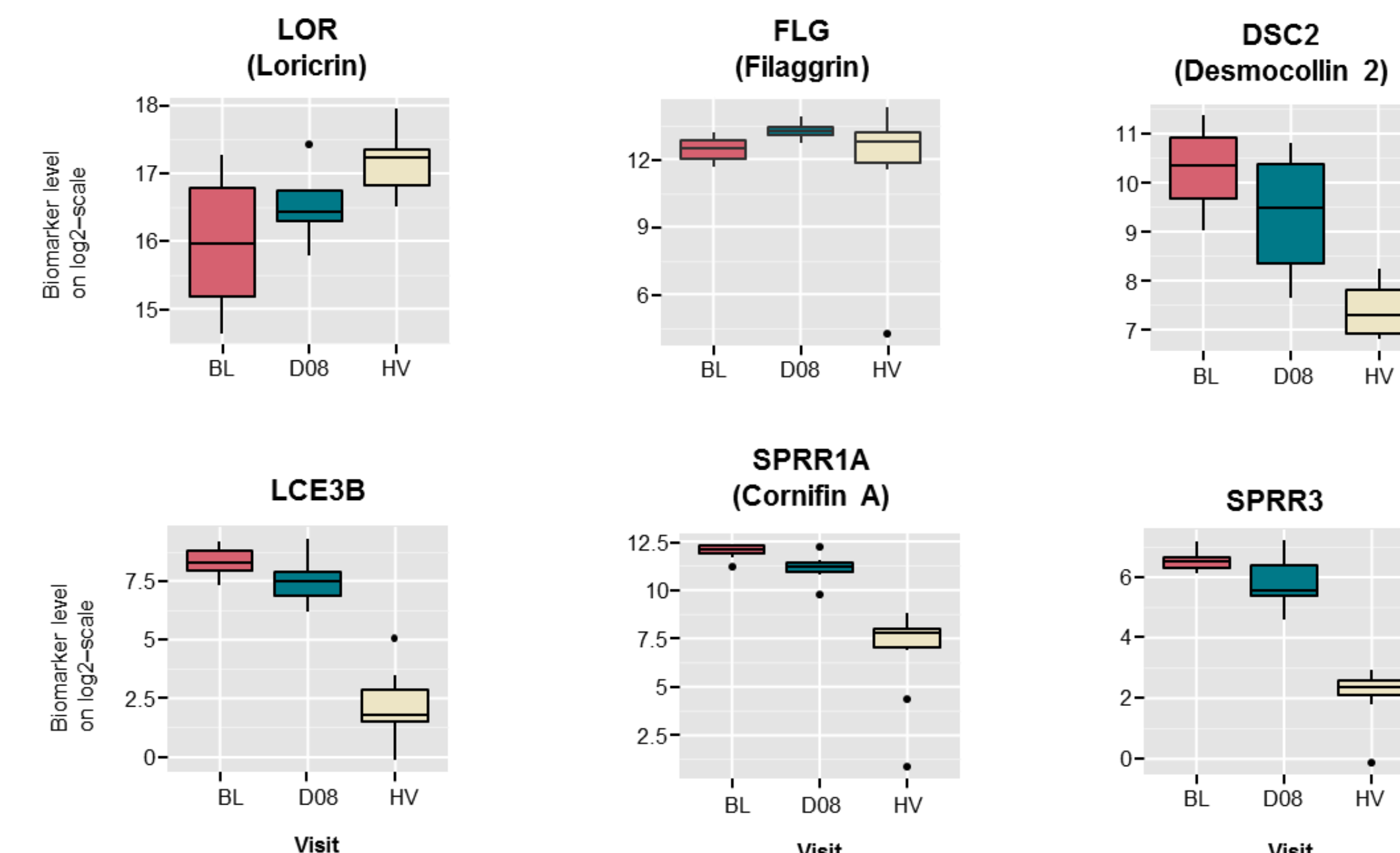
- Protein levels of amphiregulin and epiregulin, members of the EGF family of growth factors which are upregulated in psoriasis⁵ and drive autocrine keratinocyte proliferation,⁶ were reduced within 7 days of a single s.c. dose of secukinumab, particularly in the epidermis
- Secukinumab also downregulated expression of gelatinase B (MMP-9) protein, a metalloproteinase that is implicated in angiogenesis and tissue destruction and is upregulated in psoriatic plaques⁷



Data represent median (horizontal line), first and third quartiles (box) and range (vertical line). Outliers plotted as individual points. BL, baseline; D, day; dISF, dermal interstitial fluid; EGF, epidermal growth factor; MMP, matrix metalloproteinase; NL, non-lesional skin from subjects with psoriasis

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

- Secukinumab upregulated the mRNA expression of filaggrin (FLG) and loricrin (LOR), important epidermal barrier proteins that are downregulated in psoriatic skin⁸
- Secukinumab also induced positive transcriptional changes in a number of genes involved in epidermal differentiation, such as small proline-rich proteins (SPRRs), late cornified enveloped (LCE) genes and desmocollin 2 (DSC2), which are dysregulated in psoriatic skin^{9,10}



Data represent median (horizontal line), first and third quartiles (box) and range (vertical line). Outliers plotted as individual points. Quantitative values represent relative gene expression levels. BL, baseline; D, day; HV, healthy volunteer

Conclusion

- Secukinumab 300 mg sc rapidly induced positive changes in the expression of proinflammatory cytokines/chemokines, mediators of keratinocyte proliferation and markers of skin integrity and differentiation within 7 days of treatment
- Key molecular factors and processes implicated in the pathophysiology 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 proinflammatory cytokine and chemokine genes that are elevated in psoriatic skin, including IL-17A, IL-17C, IL-23A, IL-36A, CXCL1 and CXCL8
- Protein levels of amphiregulin and epiregulin, key mediators of keratinocyte proliferation, and MMP-9, which is implicated in angiogenesis and keratinocyte mobility, were also reduced at this early time point
- A reduction in keratinocyte proliferation drivers was followed by positive changes at the mRNA level in markers of skin differentiation and cornification, such as loricrin, desmocollin-2 and LCE3B
- These data provide further evidence for IL-17A being a central cytokine in the pathogenesis of psoriasis and, consistent with clinical findings from phase 3 trials, indicate that, by inhibiting IL-17A, secukinumab can induce rapid positive changes in the underlying pathophysiology of psoriasis as early as one week after treatment

References

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