BRIEF REPORT

Therapy-dependent modulation of *Staphylococcus aureus* colonization in atopic dermatitis: Insights from anti−IL-4/IL-13 and JAK inhibition

Atopic dermatitis (AD) is a chronic inflammatory skin disease driven by barrier defects, Th2-skewed immunity, and microbial dysbiosis. Overgrowth of *S. aureus* contributes to disease severity and inflammation, with colonization correlating with clinical severity.[1,2] While anti−IL-4Rα and JAK inhibitors are established systemic therapies, site-specific dynamics of *S. aureus* during treatment remain underexplored.[3-5]

We enrolled 23 adults with severe AD (baseline mean EASI 26.9 ± 6.3) received dupilumab ($n = 12$) or upadacitinib ($n = 11$); 95.7% had sensitive areas (ie face, neck, hands, and genital) involved. Clinical assessments were performed at baseline (T0), at 8 (T8), and 16 weeks (T16) of treatment. Skin swabs from 3 lesional (face, a moist area, a dry area) and 1 nonlesional site were collected concurrently. *S. aureus* was quantified by culture and PCR confirmation. Changes in clinical outcomes and bacterial abundance over time and between treatments were analyzed using linear mixed-effects models, with $P < .05$ considered significant.

All patients improved EASI score by week 16, with distinct treatment trajectories (time × treatment $P = .043$, Fig 1). Upadacitinib induced rapid EASI reduction at T8, followed by stabilization, whereas dupilumab showed gradual continuous improvement. EASI50/75/90 response rates increased over time, and they were reached by 85%, 65%, and 50% of patients at T8 increasing to 95%, 71%, and 67% at T16; and minimal disease activity was achieved in a subset of patients.

Baseline *S. aureus* abundance was highest on the face, followed by wet and dry lesional sites, and lowest at nonlesional sites. Both treatments significantly reduced bacterial levels at T8 and T16 across all sites (Fig 2; Supplementary Table I, available via Mendeley at https://www.mendeley.com/reference-manager/reader/015b90dc-6b98-3e3c-aacd-0401d9f6153e/142509df-b8d3-9bbb-0729-891c48f45359). Linear mixed-effects models confirmed significant effects of time ($P < .001$), treatment ($P = .007$), and body site ($P = .018$), with parallel trends across therapies. EASI scores correlated positively with

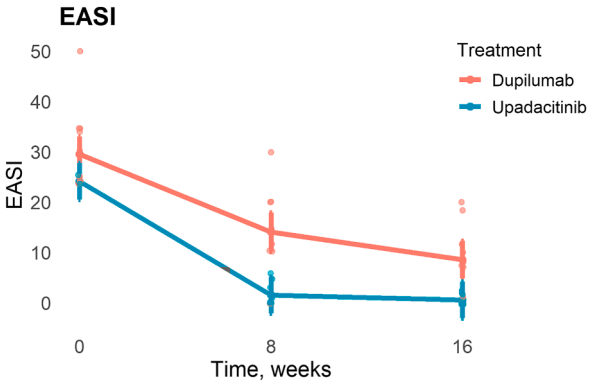

Fig 1. EASI score over time, stratified by treatment group. Mean EASI values and 95% confidence intervals are shown at baseline (T_0), week 8 (T_8), and week 16 (T_{16}) for patients treated with dupilumab (coral red) and upadacitinib (turquoise). Estimates derive from a linear mixed-effects model with fixed effects for time, treatment, and interaction, and a random intercept for subjects to account for intraindividual correlation. All upadacitinib patients achieved EASI50 and EASI75 at both timepoints.

S. aureus abundance, with moderate-to-strong repeated-measures correlations in lesional areas. Mixed-effects modeling indicated that a 10-unit increase in *S. aureus* count was associated with a 2.6-point increase in EASI score ($P < .001$), independent of treatment and site.

Overall, both dupilumab and upadacitinib effectively reduced disease severity and *S. aureus* abundance across lesional and nonlesional sites, with upadacitinib showing faster clinical improvement. Bacterial colonization differed between nonlesional and lesional skin and, within lesional areas, further varied across the face, moist, and dry sites, likely reflecting differences in skin structure and the associated microenvironmental characteristics of these anatomical locations. Reduction in *S. aureus* paralleled clinical improvement, suggesting that controlling inflammation indirectly modulates microbial dysbiosis rather than through direct antibacterial effects. These findings underscore the role of targeted immunomodulation in restoring skin homeostasis and highlight the potential for personalized, site-specific interventions in AD.[1-5]

In conclusion, our study highlights site-specific *S. aureus* colonization in AD, with highest loads in seborrheic areas (such as the face), and shows that reductions parallel clinical improvement with dupilumab and upadacitinib. While effects on the broader microbiota remain unknown, these findings support personalized, site-specific therapeutic strategies and further exploration of skin microbiome−immune interactions.

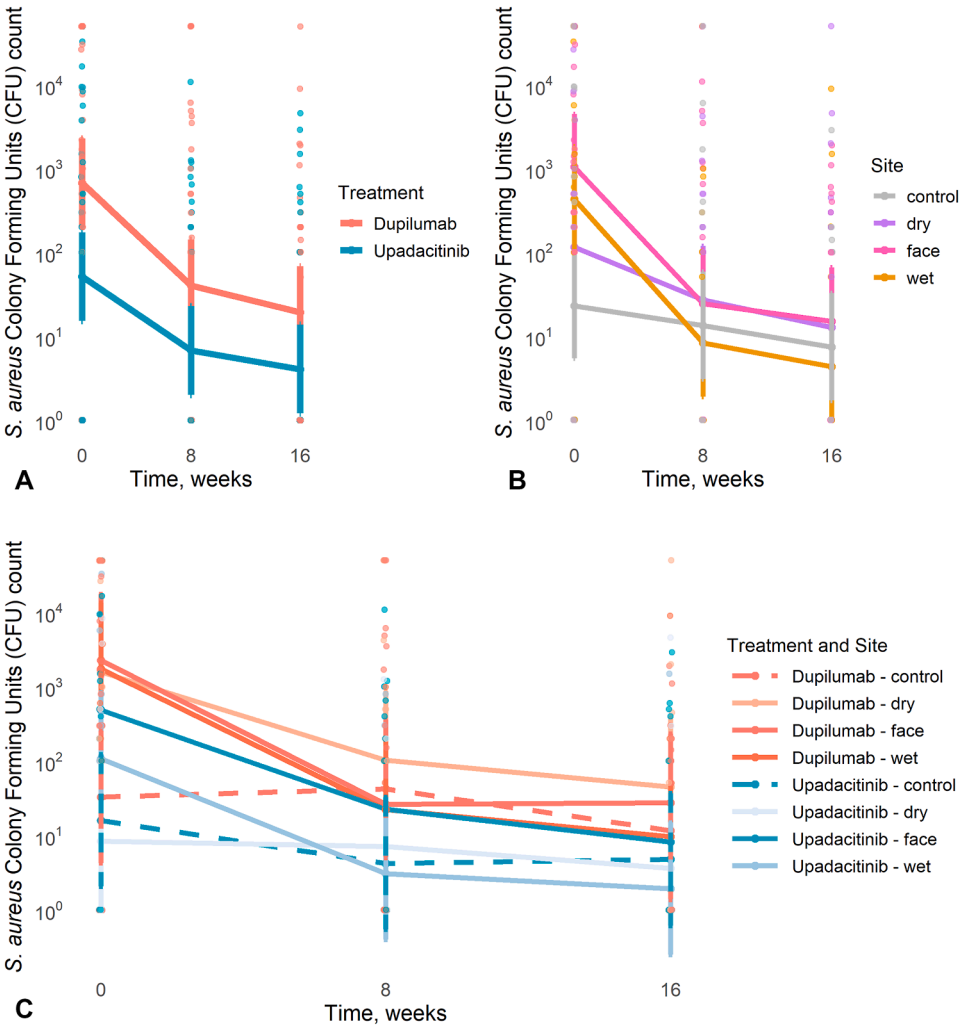

Fig 2. *S. aureus* CFU counts overtime, shown separately by treatment (**panel A**), site (**panel B**) and overall (**panel C**). **A,** Mean CFU values and 95% confidence intervals are shown at baseline (T_0), week 8 (T_8), and week 16 (T_{16}) for patients treated with dupilumab (*hot pink*) and upadacitinib (*light green*). **B,** Mean CFU values and 95% confidence intervals are presented at baseline, week 8, and week 16 for control site (*light grey*), dry area (*light green*), face (*hot pink*), and wet area (*amber*). Marginal and complete estimates were obtained from a linear mixed-effects model including fixed effects for time, treatment, site and their interaction, and a random intercept for subjects to account for intraindividual correlation. **C,** Overall patient's mean CFU values and 95% confidence intervals are shown at baseline, week 8, and week 16 for treatment with dupilumab and upadacitinib and site [Dupilumab: control area (*coral red-dashed*), dry area (*light salmon*), face (*coral red*), and wet area (tomato red); upadacitinib: control area (*turquoise-dashed*), dry area (*pale sky blue*), face (*turquoise*), and wet area (*light blue*)].

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Patient consent: This study was conducted in accordance with ethical standards and guidelines for research involving human participants. Written informed consent was obtained from all participants prior to inclusion in the study. Participants were informed of the study purpose, procedures, risks, benefits, and their right to withdraw at any time without consequence. All personal health information has been handled confidentially and anonymized to protect participant privacy.

IRB approval status: The study was approved by the local ethics committee (CE 411/2023).

Key words: atopic dermatitis; dupilumab; IL-4/IL-13 blockade; JAK inhibitor; skin microbiome; Staphylococcus aureus; upadacitinib.

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Conflicts of interest

None disclosed.

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