

redness as AE. Furthermore Pt.8, who was also under treatment with CsA at T0, experienced a serious AE (SAE) 3 days after induction. Malaise and fever arose due to the development of multiple dental abscesses, prompt hospitalization was necessary. Imaging made evident the presence of background multiple destructive caries from which the abscesses derived. Even if SAE was not considered associated to dupilumab, no second inductive dose at T1 was performed opting for administration of 300 mg after 4 weeks, with no further problems detected. No ophthalmologic AE was registered from T0 to T3.

The approval of dupilumab in the treatment of adolescents with moderate-to-severe AD increased the therapeutic options available for the treatment of this disease.^{7,8} Recently also children from 6 to 11 years old were eligible for this therapy. The reference phase III study conducted by Paller et al.¹ concluded for a high safety and efficacy profile of dupilumab for this age group; however, real-life observations are still limited. Data exposed have shown a general improvement of disease severity scores and quality of life, even if below the line of LIBERTY AD PEDS.¹ Our population consisted of a majority of children under systemic immunosuppressants and included two patients who developed not only a known AE,⁹ namely, facial redness, but also a SAE, which required hospitalization. These observational data should be validated by larger studies.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

Informed consent

The patients in this manuscript have given written informed consent to publication of their case details.

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Data availability statement

Data available on request due to privacy/ethical restrictions.

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Basic skin therapy effects on skin inflammation and microbiome composition in patients with atopic dermatitis after challenges with grass pollen

Dear Editor,

This mono-centre, randomized, open-label, observer-blinded parallel-group study (clinicaltrials.gov; NCT03315611) was initiated to study effects of emollients on skin inflammation in atopic dermatitis (AD) upon grass pollen exposure in moderately to highly grass pollen IgE-sensitized patients (approved by the Ethics committee MHH, no. 7586). In a preceding randomized, controlled study (NEUROP), repetitive grass pollen exposure led

to a significant flare-up in AD patients using an allergen challenge chamber (ACC).¹ We used the same model for allergen challenge (AC) with *Dactylis glomerata* pollen (Allergon AB, Ängelholm, Sweden) in nine patients whose skin was (pre-)treated from day -7 until day 5 of follow-up with 'Eucerin AtopiControl LOTION' and 'Eucerin AtopiControl Gesicht-screme' twice daily (Treatment group) and seven patients who did not apply any basic therapy (Control group).

In the treatment group, IL-13 expressing cells were reduced in numbers and also regarding expression intensity, which was mostly pronounced in the epidermis (Fig. 1a–d), and CRTh2 expression was reduced significantly and most prominently in the *Stratum papillare* (Fig. 1e–g). Moreover, we observed that the treatment of the skin surface influenced the microbial composition as detected by 16S rRNA gene sequencing with significantly less intra-individual bacterial beta diversity, that is, community (dis-)similarity, but similar alpha diversity, in the Treatment group compared with the Control group before and after AC (Fig. 2a–d). In the Treatment group, the amplicon sequence variant 1 (ASV1) (*Staphylococcus* (unc.) 1, 100%

identity with *S. epidermidis*) significantly increased after challenge ($P = 0.022$), while an increase trend in ASV3, which most probably resembles *S. aureus*, was observed for several donors of the Control group (Fig. 2e). The emollients applied in our study contain the ingredient licochalcone A (LcA), which led to a reduction in *S. aureus* skin colonization after 7 days of topical application in a previous study.² The species *S. epidermidis*, detected in elevated frequencies in the Treatment group after AC, is commensal and is often referred to as an antagonist of *S. aureus*,^{3,4} less disease-driving compared to *S. aureus*,⁵ and even beneficial.⁶ Although single strains of *S. epidermidis* can also act in a pro-inflammatory manner under certain conditions, it has been proposed that higher frequencies of this species on AD skin rather point towards an improvement of the disease.⁷

After AC, we observed slight increases of the SCORAD in both study groups by trend but no significant differences between both study groups (data not shown). Previous studies showed that lymphocytic infiltration takes place also in normal looking skin in AD,⁸ and that pro-inflammatory cytokines, especially of the type-2 are upregulated in non-lesional skin (concept

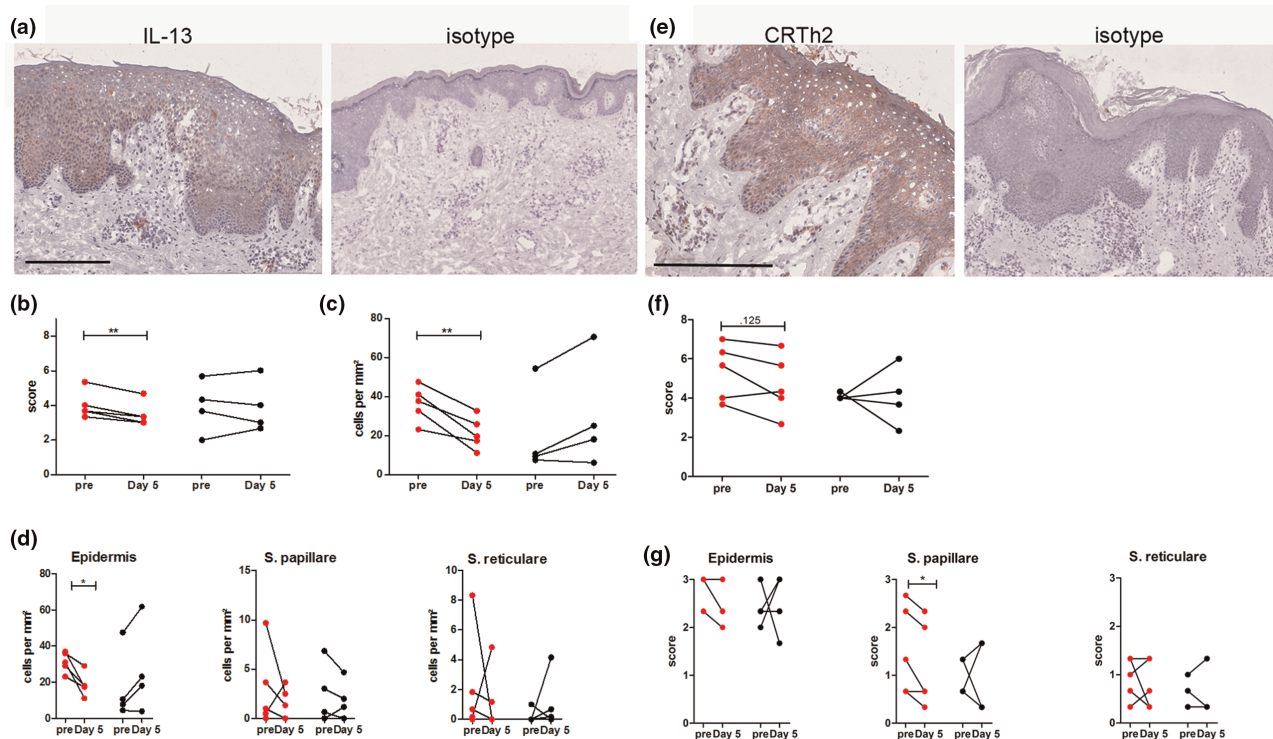


Figure 1 Expression of IL-13 (a–d) and CRTh2 (e–g) in lesional AD skin assessed by immunohistochemistry from screening day to post-challenge day 5. a, e, exemplary stainings of skin sections. b, f, sum of scores of epidermal, *S. papillare* and *S. reticulare* staining. 0 = no staining, 1 = light, 2 = intermediate, 3 = strong staining. c, number of counted cells per 1 mm². d, g, number of counted cells per 1 mm or score separated for epidermis, *S. papillare* and *S. reticulare*. Red: Treatment group; black: Control group. Scale bar: 250 µm. (Paired t-test).

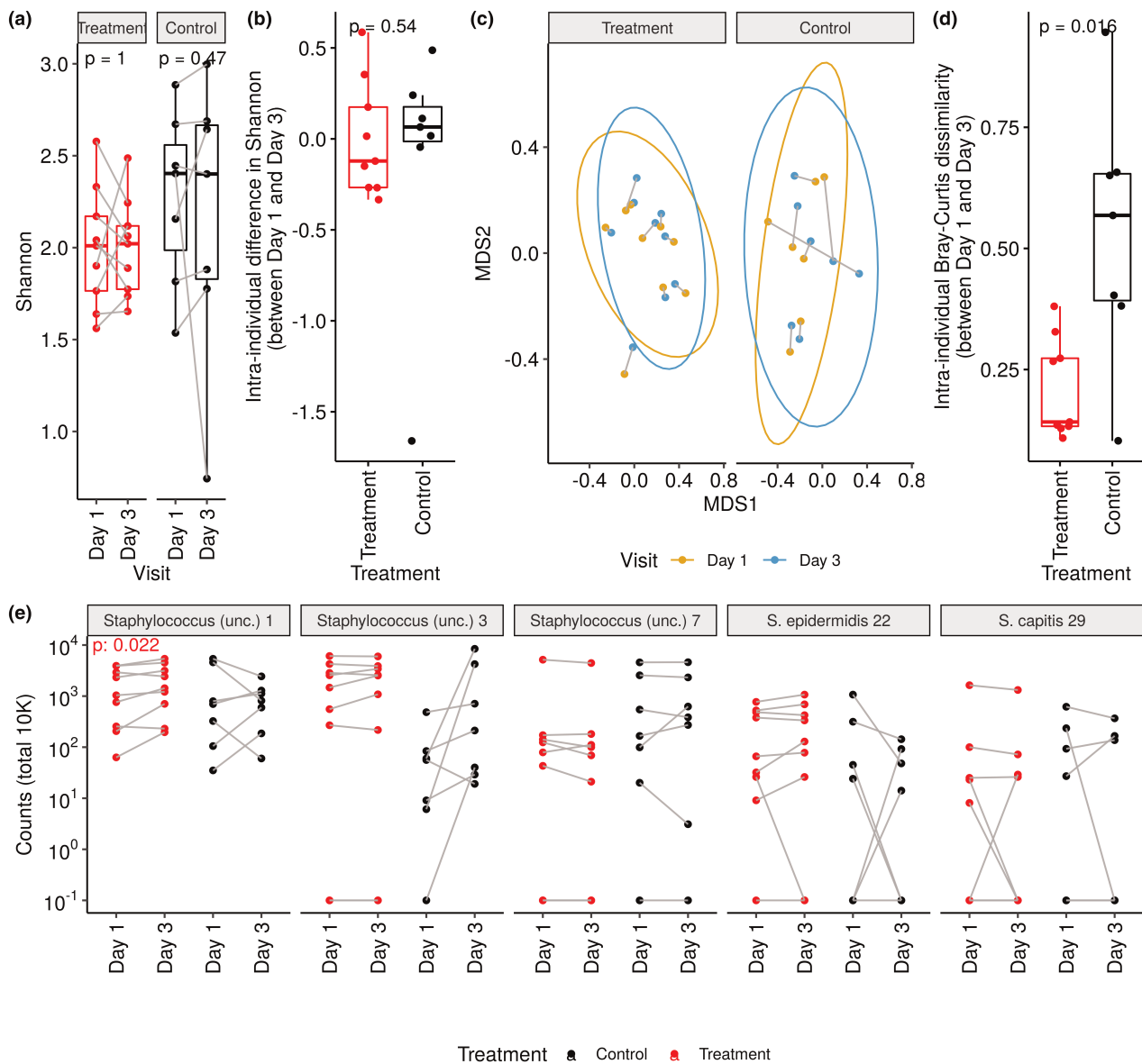


Figure 2 Skin microbiota profiles from pre-challenge Day 1 to post-challenge Day 3. a,b Alpha-diversity was estimated with Shannon index. No difference in alpha diversity between days was observed within each group (a), or intra-individually between day 1 and day 3 (b) ($P > 0.05$, paired Wilcoxon test). c, Beta diversity was estimated from Bray-Curtis dissimilarities and visualized using Non-metric Multidimensional Scaling (NMDS). d, Lower intra-individual Bray-Curtis dissimilarity was observed in the Treatment group in comparison with the Control group ($P < 0.05$, Wilcoxon test). e, to avoid multiple testing, we decided to investigate the differences between day 1 and day 3 in ASV abundances of the five most abundant *Staphylococcus* ASVs, which still represented 45% of total sequences recovered. An increase in abundance was observed in ASV1 (*Staphylococcus* (unc.) 1, 100% identity with *S. epidermidis*) in Treatment group between day 1 and day 3 ($P < 0.05$, likelihood-ratio test). No significance was observed for changes in the Control group or any other most abundant *Staphylococcus* ASVs. For better visualization, samples were rarefied to 10 000 sequences and 0.1 was added to read counts. Y-axis is at log scale. Unclassified (unc.) is abbreviated.

of ‘microinflammation’) compared to healthy skin.^{9,10} Our findings suggest that the application of basic skin care before and during AC with grass pollen in the controlled setting of the ACC leads to beneficial effects on emerging lesions of AD.

Because visual effects on severity of AD may have been masked by the small number of participants in the current study we performed a combined analysis adding the results from patients from our previously published NEUROP¹ study applying the same

challenge protocol with grass pollen and which could therefore be integrated into the control group. With sample sizes of nine patients in the Treatment group and 13 patients in the 'extended' control group significantly higher increases of objective SCORAD and of local air-exposed SCORAD upon allergen challenge were observed in the 'extended' control but not in the Treatment group (data not shown). Taken together, this is the first study to elucidate effects of basic therapy on allergen-induced skin inflammatory immune responses and on the skin microbiome in AD.

Conflict of interest

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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