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ORIGINAL ARTICLE

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Topical *S. aureus*-Targeting Endolysin Significantly Improves Symptoms and QoL in Individuals With Atopic Dermatitis

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ABSTRACT

Atopic dermatitis (AD) is a chronic skin condition affecting an increasing number of children and adults whose quality of life is impacted by chronic itch and pain. It is characterized by an altered epidermal barrier, skin inflammation, and skin microbiome dysbiosis particularly over-colonization of *Staphylococcus aureus*. The efficacy and tolerance of a cream containing a *S. aureus*-targeting technology (endolysin) was assessed in an open-label, two-week study in children and adults with mild-to-moderate atopic dermatitis. A total of 43 patients ranging from 7 months to 57 years old were included and all patients finished the study without any tolerance problem. Disease severity, measured with SCORAD, quickly reduced by 43% in 7 days and by 68 % in 14 days. The benefit was perceived by the whole panel with a marked improvement in overall QoL. This study shows the efficacy of a highly specific *S. aureus*-targeted technology in alleviating symptoms and improving QoL in children and adults with atopic dermatitis. It could also be beneficial in reducing and preventing flares in subjects with *S. aureus* load due to its good tolerance and specific action.

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INTRODUCTION

Atopic dermatitis (AD) affects 20% of infants and adolescents and up to 3% of adults worldwide[1,2] and its incidence is increasing globally.[3] AD causes erythema, constant intense itching,[4] and psychological distress[5] which negatively impacts quality of life (QoL) more than other chronic conditions such as heart disease or diabetes.[6] In children, it has the second highest impact on QoL.[7]

AD is a chronic inflammatory skin condition associated with epidermal barrier dysfunction, abnormal immune response, and skin microbiome imbalance.[8] These three factors are interdependent thus enabling AD symptoms to be managed from multiple angles. Skin microbiome dysbiosis is often characterized by low skin microbial diversity compared to healthy skin and an over-colonization of *S. aureus*.[9] *S. aureus* levels are associated with AD disease severity, flare frequency and symptoms that directly impact QoL.[10-12] Its toxins stimulate proinflammatory cytokine and chemokine production causing itching, burning sensations, and pain,[13,14] and create a vicious itch-scratch cycle.[15-17]

During AD flares, treatment aims to reduce inflammation and itching, rebuild the epidermal barrier, and prevent secondary infections.[18] Appropriate moisturizers and cleansers are the cornerstones of AD management to address skin barrier dysfunction.[19] Topical corticosteroids (TCS) are first-line treatment for flares since they effectively reduce inflammation.[20] However, their use is limited to avoid developing skin atrophy in sensitive skin areas.[21] Furthermore, patients express concerns (corticophobia) which can impact TCS use, adherence to treatment and overall effectiveness.[22] Secondary infection, particularly by *S. aureus*, can be treated with broad spectrum or anti-staphylococcal antibiotics[20] but these can damage the beneficial skin microbiota and potentially lead to antibiotic resistance.[23] Considering the mounting evidence pointing towards the major negative role of *S. aureus* in AD and the beneficial role of the skin microbiome for skin homeostasis, a treatment exclusively targeting *S. aureus* offers many advantages.[24]

Many microbial ecosystems, including the skin microbiome, harbor viruses called bacteriophages that only infect bacteria.[25] Bacteriophages are specific for their target bacteria, and at the end of their lytic cycle induce the production of enzymes, called endolysins, which degrade the peptidoglycan of the bacterial cell wall from within, causing cell lysis and progeny virion release. Since Gram-positive bacteria, such as *S. aureus*,

lack an outer membrane, the peptidoglycan is exposed and the appropriate endolysin applied externally can perforate the cell wall resulting in osmotically driven lysis and bacterial cell death.[26]

Endobioma™ is a recombinant chimeric protein derived from naturally occurring endolysin designed to be highly effective against *S. aureus*. Its structure combines a cell wall binding domain that specifically recognizes *S. aureus* peptidoglycan motifs and two enzymatically active domains that lyse them. Low doses of Endobioma have been shown to quickly eliminate *S. aureus*, including antibiotic resistant strains such as MRSA.[27,28] Other typical commensal skin residents, even from the staphylococci genera such as *S. epidermidis*, are left unaffected.[27,29]

The aim of this study was to evaluate the efficacy (disease severity and QoL) and tolerance of a cream containing Endobioma applied for two weeks in adults or children with mild-to-moderate atopic dermatitis.

MATERIALS AND METHODS

Study Product

The study product contained Endobioma, also known as Staphefekt™ SA.100, kindly provided by Micreos Human Health (Bilthoven,The Netherlands) in a 0.0035% simplex cetomacrogol formula.

In vitro Efficacy Against *S. aureus*

To evaluate the antimicrobial activity of the study product, a small aliquot was inoculated and homogenized with a suspension of *S. aureus* ATCC 6538 to achieve a final concentration of 10^6 colony forming unit (CFU) per gram of product. After 30- and 60-minutes contact time at room temperature, the mixture was neutralized to stop enzymatic activity. Serial dilutions were plated on Eugon LT100 agar plates, incubated at 35°C for 48 hours, and surviving *S. aureus* colonies on the plates counted.

In vivo Study Design

An open-label, interventional, clinical study was conducted in South Africa from September to October 2018, according to the Helsinki Declaration (1964) and its successive updates. Participants replaced their normal cream with the study product and applied it on all body lesions as needed but at least once daily for two weeks. Lipikar Syndet AP+ was provided for daily cleansing.

Participants

Patients were recruited from the IEC (Institut d'Expertise Clinique) database. To be included, male or female Caucasian adults (aged 18 to 70 years) or children (aged 3 months to 12 years) presented an AD diagnosis meeting Hanifin's criteria (>3 basic features and >3 minor features), with AD present for at least 6 months prior to inclusion (SCORAD >30 at inclusion).

Measurements

Clinical examinations were performed at baseline, day 7 and day 14. Cutaneous acceptability was assessed by observing physical signs (including erythema, oedema, dryness, desquamation) linked to the study product and questioning about functional signs (including tingling, tightness, and burning sensation) at baseline, day 3 (by phone), 7, and 14. The participants reported their nature, location, intensity, duration, period of appearance after product application. Application number and frequency were also reported.

On days 0, 7 and 14, disease severity was clinically evaluated using SCORAD (SCORing Atopic Dermatitis), and local SCORAD at defined areas. Standardized pictures of the AD lesion were taken on days 0, 3 (by the subject), 7, and 14, focusing on the lesion used for Local SCORAD. Participants completed Patient-Oriented SCORAD (PO-SCORAD) and ranked pruritus, tingling, and burning sensation on a scale from 0 (absent) to 3 (severe) on day 0, 3, 7, and 14. QoL was measured using DLQI (Dermatology Life Quality Index) and CDLQI (Children's Dermatology Life Quality Index) questionnaires on days 0, 3, 7, and 14.

Data Analysis

Mean and standard deviation were calculated for individual data at each time point and compared to baseline values. Significance thresholds were $P<0.05$ and $P<0.01$ for Shapiro-Wilk test. Distribution normality was checked with Shapiro-Wilk test, if distribution was normal, paired Student t-test was applied, and if not, the Wilcoxon test was used. Any statistically significant changes were reported with their corresponding variation from the individual percentage mean. Percentage of patients with improvement was calculated.

RESULTS

In vitro results showed that 1g of Endobioma formula rapidly inactivated 10^6 CFU of *S. aureus*. Within 30 minutes, 99.99 % of the bacteria were killed and the limit of detection was achieved after one hour. (Figure 1 >4-log CFU reduction)

FIGURE 1. Time-kill assay. Endobioma™-formula vs placebo.

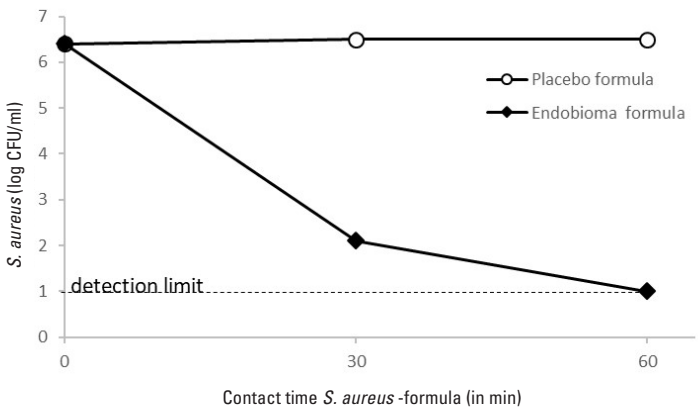


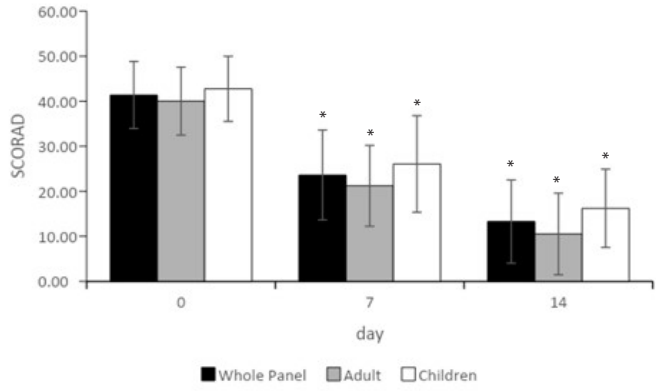
TABLE 1.

Panel Demographic			
	Whole Panel	Adult Panel	Children Panel
Patient, n	43	22	21
Female, n (%)	29 (67%)	19 (86%)	10 (48 %)
Male, n (%)	14 (33%)	3 (14%)	11 (52 %)
Mean age (min-max) years	20 (0.58-57)	33.7 (18-57)	5.7 (0.58-12)
SCORAD at baseline average ± SD	41.36 ±7.45	40.03 ±7.57	42.75 ± 7.24

In total, 43 people [22 adults (mean age, 33.7) and 21 children (mean age, 5.7)] were included and completed the clinical study, all presenting comparable disease severity at baseline (see SCORAD -Table 1). The participants reported applying the study product two to three times daily on average during the study period.

Overall, the study product was well tolerated, and no adverse events related to it occurred. Nine participants reported some cutaneous discomfort, redness, small pimples, or dryness, which were judged to be expected and frequently encountered in patients with mild AD.

FIGURE 2. Mean SCORAD scores with Endobioma™-containing cream in whole, adult, and children panels. Error bars indicate standard error of the mean.



*P<0,001 vs D0

The study product rapidly reduced disease severity in a

TABLE 2.

Clinical Scoring of Disease Severity Progression Over the Two-Week Study Period –Whole Panel (n=43)						
Clinical scoring of disease severity	Baseline Mean ± SD	Day 7 Mean ± SD	Day 14 Mean ± SD	D7/D0 variation	D14/D0 variation	% Patients with improvement at day 14
Score A (Extent)	14.6± 12.8	8.1*± 8.6	5.5*± 6.1	-39%	-58%	91%
Score B (Intensity)	6.5± 1.6	3.6*± 1.6	2.3*± 1.6	-44%	-65%	95%
Pruritus	7.8± 1.5	4.6*± 2.5	2.1*± 2.2	-41%	-74%	98%
Sleep loss	7.7± 1.6	4.7*± 2.5	2.1*± 2.1	-40%	-74%	98%
SCORAD Index	41.4± 7.5	23.6*± 10.1	13.3*± 9.2	-43%	-68%	100%
Local SCORAD	9.2 ± 1.7	5.3* ± 2.2	3.1* ± 2.2	-42%	-67%	100%

*P< 0.001 versus Baseline

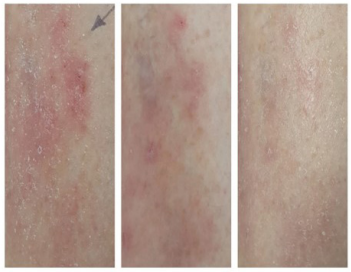
TABLE 3.

Self-Assessment Results Including PO-SCORAD and Skin Sensitivity Results –Whole Panel.				
	Baseline	Day 3	Day 7	Day 14
PO-SCORAD				
Mean ± SD % variation	49.9 ± 13.7	43.4 ±16.0** -11%	35.7 ± 17.0* -30%	25.7 ± 16.8* -50%
% patients with improved PO-SCORAD	--	65%	91%	100%
Skin sensitivity questionnaire				
Pruritus sensation Mean ± SD % variation	2.58 ± 0.50	1.86 ± 0.83* -26 %	1.84± 0.72* -29%	1.26 ± 0.88* -51 %
Tingling sensation Mean ± SD % variation	2.16 ± 0.75	1.33 ± 0.89* -33%	1.26 ± 0.66* -41%	0.74 ± 0.69* -63%
Burning sensation Mean ± SD % variation	2.4 ± 0.73	1.23 ± 0.95* -47%	1.33 ± 0.94* -46%	0.56 ± 0.83* -79%

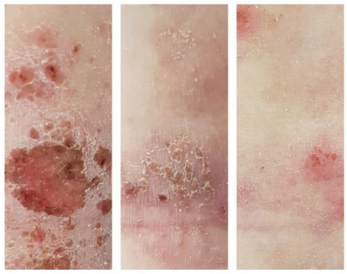
*P<0.001, **P<0.005

FIGURE 3. Pictures of lesions treated with the Endobioma™-containing cream at baseline, day 7, and day 14 in an adult subject (3A) and a child (3B).

(3A) Subject nb41. SCORAD from 11 at Baseline to 2 at D14

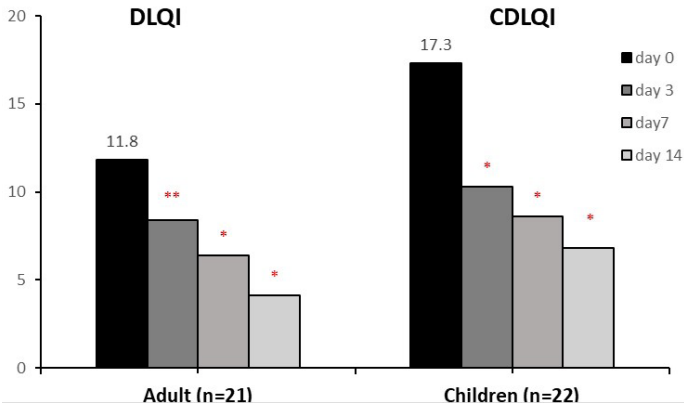


(3B) Subject nb38. SCORAD from 12 at Baseline to 5 at D14



statistically significant and clinically relevant manner over the two-week study. SCORAD scores reduced by an average of 43% (day 7) and 68% (day 14) compared to baseline (Figure 2). The treatment was equally effective in both adults and children with all patients improving by day 14. Similarly, local SCORAD reduced by 42% at day 7 and 67% at day 14 compared to baseline (Table 2). Visible lesion resolution is shown in Figure 3. Notably, as early as day 3, patients reported a statistically significant decrease in PO-SCORAD (Table 3). PO-SCORAD further decreased by an average of 30% (day 7) and 50 % (day 14) with all participants reporting better scores by day 14. More specifically, skin discomfort significantly improved by day 3 in both adults and children, with itching decreased by 51%, tingling by 63% and burning by 79% at day 14 (P<0.005 vs baseline) (Table 3).

FIGURE 4. Quality of life assessments.



*P<0.001, **P<0.01

The reported improvements translated into a significantly increased QoL for all participants: 100% of children and 95% of adults reported a higher QoL on day 14 with DLQI reducing from 11.8 ± 5.4 to 4.1 ± 4.0 in adults and CDLQI from 17.3±5.4 to 6.8±5.3 in children (P<0.001 vs baseline) (Figure 4, Table 4).

Participants reported a good cosmetic acceptability. After just 7 days, 98% of participants reported that the study product left a protective film on the skin and the skin felt comfortable. By day 14, all patients agreed that the study product was easy to apply with 91% wanting to continue using it.

DISCUSSION

For the first time, our study demonstrates the efficacy of an anti-*S. aureus* product in children and adults with AD. With Endobioma monotherapy, both clinicians and participants including children reported significantly improved skin sensitivity, PO-SCORAD and overall QoL. A recent Cochrane review[30] analyzed studies aiming to reduce *S. aureus* in AD patients and failed to correlate anti-staphylococcal intervention with improvement in symptoms and QoL especially in children. However, our results suggest that a precision ingredient like Endobioma alone could be a potential alternative to traditional

TABLE 4.

DLQI/CDLQI Results

	Baseline Mean ± SD	Day 3 Mean ± SD	Day 7 Mean ± SD	Day 14 Mean ± SD	D3/D0 variation	D7/D0 variation	D14/D0 variation	Patients with improvement on day 3	Patients with improvement on day 7	Patients with improvement on day 14
DLQI Adults N=21	11.8 ± 5.4	8.4**± 5.2	6.4* ± 3.8	4.1* ± 4.0	-26%	-42%	-63%	76%	86%	95%
CDLQI Children N=22	17.3 ± 5.4	10.3* ± 6.8	8.6* ± 5.9	6.8* ± 5.3	-43%	-51%	-61%	82%	91%	100%

*P<0.001, **P<0.01

treatments in AD adults and children. Using Endobioma as adjunctive therapy to boost efficacy of medical treatments and potentially reduce their length of use would be interesting and should be further investigated.

In this era of increasing antibiotic resistance, Endobioma mechanism of action makes it an attractive, precise, antimicrobial solution.[31] The recognition and lytic activity are highly specific to *S. aureus* cell wall, excluding impact on other bacteria even within the same genus.[32,33] Unlike antibiotics, Endobioma has little risk of developing resistance.[26] Resistance mechanisms such as active efflux from the cell or decreased membrane permeability are avoided due to the external application.[34] Moreover, *S. aureus* membrane peptidoglycans is a highly preserved structure, difficult to alter. Last, Endobioma-triggered cell wall destruction is independent of host metabolism, so there is no pressure for the bacteria to evolve.[27]

Our study adds new evidence to the potential and current trend to target the skin microbiome for AD management as we further understand the role of skin microbiome dysbiosis and *S. aureus* in its pathogenesis.[11] Though follow-up studies should be conducted to assess the effect of Endobioma on the skin microbiome composition, our results both show the rapid anti-*S. aureus* activity of the cream in vitro and its efficacy in managing AD in vivo.

The clinical improvements shown in this study confirm previous, preliminary case report of three cases of recurrent *S. aureus*-related dermatoses that were successfully treated with the endolysin-containing cream.[35] When used in a double-blind, vehicle-controlled study in conjunction with TCS, the endolysin-cream failed to demonstrate an effect on corticosteroid use (MAAS study).[35] However, prior to inclusion, patients were treated for 2 weeks with a moderate TCS dose, dramatically reducing their AD severity, and could continue using TCS with the endolysin-cream. Both factors could have contributed to masking the full benefit of endolysin vs vehicle. For those reasons and to really gauge the benefit of this new technology, we chose to use the Endobioma-containing cream as a monotherapy in patients with a higher initial SCORAD.

Of interest is the rapidity of the benefits observed with Endobioma. SCORAD was reduced by 43% after 7 days and 68% by 14 days. In a similar study design, the Eczema Area Severity Index (EASI) and the Atopic Dermatitis Severity Index (ADSI) were reduced by 51% and 54% after 2 weeks.[36] Although numerical improvement comparison is difficult with different scoring scales, our study showed an itch severity reduction of 74% at day 14 compared to 61% in the other study.

Poor adherence to AD treatment associated with side effects, treatment length or "corticophobia", is a known problem and can lead to *S. aureus* recolonization and flares.[37] Rapidly effective, TCS-free, with an inherent respect for the skin microbiota, and without observed side effects, Endobioma cream represents an attractive AD treatment solution. Additionally, our study highlighted a good cosmetic acceptability which may improve treatment compliance, potentially reducing flares. Interestingly, in the MAAS study[38] the number of doctor-reported flares was lower in the Endobioma group than in the vehicle group. Altogether, these results suggest that it would be worth assessing the long-term benefits of Endobioma as a proactive therapy to prevent and reduce the occurrence of flares and assess compliance.

CONCLUSION

This study showed that *S. aureus*-targeting Endobioma cream monotherapy produced a statistically and clinically significant reduction of AD severity scores and improved skin sensitivity and QoL in both adults and children. Safety and tolerability were excellent, enabling Endobioma to be applied to sensitive areas, thus, constituting a good option for AD patches in children. Future investigation assessing the *in vivo* effect of Endobioma-cream on the skin microbiome, particularly *S. aureus*, and immune response markers would be interesting to further understand the interplay between skin microbiome, skin immune response and AD clinical symptoms occurrence. Since Endobioma-cream is safe and offers an opportunity to prevent *S. aureus* over-colonization, it may be beneficial to prevent and reduce flares.

DISCLOSURES

Ann'Laure Demessant, Magali Moreau, Sophie Seité, Luc Aguilar, Olivier Da Cruz and Julia Puech are L'Oréal employees. Johan Frieling is a Micreos Human Health employee.

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