Skin Pharmacology and Physiology

Skin Pharmacol Physiol , DOI: 10.1159/000547835
Received: March 26, 2025
Accepted: July 31, 2025
Published online: September 6, 2025

Effects of a gel containing the defined microalgae extract Spiralin® on the skin microbiome and clinical activity in atopic dermatitis – a double-blind, intraindividual vehicle-controlled proof-of-concept study

Reich K, Trettel N, Reich JLK, Sorbe C, Bickert T, Hartmann J, Harder I, Gerdes S, Weidinger S

ISSN: 1660-5527 (Print), eISSN: 1660-5535 (Online)
https://www.karger.com/SPP
Skin Pharmacology and Physiology

Brief Report

Effects of a gel containing the defined microalgae extract Spiralin® on the skin microbiome and clinical activity in atopic dermatitis – a double-blind, intraindividual vehicle-controlled proof-of-concept study

Kristian Reich[1], Natalie Trettel[2], Jeremias L. K. Reich[3], Christina Sorbe[2], Thomas Bickert[2], Jan Hartmann[4], Inken Harder[4], Sascha Gerdes[4], Stephan Weidinger[4]

[1] Translational Research in Inflammatory Skin Diseases, Institute for Health Care Research in Dermatology and Nursing, University Medical Center Hamburg-Eppendorf, Germany
[2] Institute for Health Care Research in Dermatology and Nursing, University Medical Center Hamburg-Eppendorf, Germany
[3] Oxford University Clinical Academic Graduate School, Oxford University, Oxford, United Kingdom, presently at McKinsey & Company, Inc.
[4] Department of Dermatology, University Clinic Schleswig-Holstein, Campus Kiel, Germany

Short Title: *Sp. platensis* microalgae extract in atopic dermatitis

Corresponding Author:
Prof. Dr. med. Kristian Reich
E-mail address: k.reich@uke.de

Keywords: atopic dermatitis, skin microbiome, Spiralin®, immune system

Abstract

Introduction: Changes in the skin microbiome in atopic dermatitis include a reduced bacterial diversity and increased abundance of *Staphylococcus aureus*. Topical antibiotics and antiseptics may decrease bacterial pathogens but lack positive effects on microbiome diversity.

Methods: In this double-blind, intraindividual vehicle-controlled proof-of-concept study, n = 20 patients received a gel containing a defined extract (Spiralin®) of the microalgae *Spirulina platensis*, previously shown to exert anti-microbial effects, or vehicle on target lesions of similar size and clinical activity. The Shannon index reflecting □-diversity and the abundance of *S. aureus* were calculated from the analysis of 16s rRNA gene libraries with untreated non-lesional skin serving as control. Clinical activity was determined by the Target Lesion Severity Score (TLSS) and lesion size.

Results: Positive effects of the active gel on the microbiome after 4 weeks of treatment were indicated by a significant increase of the Shannon index in areas treated with verum (mean increase 16.7%; $p<0.01$ vs. baseline), but not in areas treated with vehicle. This increase in verum-treated lesions was more pronounced in lesions with an at least 50% (26.3%) or an at least 75% reduction of the TLSS (33.3%). There was also a stronger decrease of the abundance of *S. aureus* in lesions treated with active gel compared to those treated with vehicle (25.5% vs. 9.4%), but significance was not met. There were several trends indicating clinical effects of the active gel. For example, vehicle-treated areas showed no reduction in area size (77.8 cm^2 at week 4 compared to 77.0 cm^2 at baseline), while verum-treated lesion area decreased on average by 6.9 cm^2. Active and vehicle gel were well tolerated and very few local side effects were noted.

Conclusion: These preliminary results indicate a positive effect of a gel containing Spiralin® on the skin microbiome in patients with active atopic dermatitis (AD) lesions combined with reductions in clinical disease activity supporting further investigations of the active gel alone or in combination with anti-inflammatory treatments in larger AD studies.

Introduction

Interactions between the skin microbiome and immune system play a relevant role in cutaneous health and disease. In atopic dermatitis (AD), barrier dysfunction, immune dysregulation and changes in the skin microbiome are considered as the main pillars of pathophysiology [1]. In particular, a reduction of microbiome diversity and increased abundance of *Staphylococcus aureus* has been reported to precede flares of AD and improvement of AD in response to anti-inflammatory therapies is often associated with a normalization of the microbiome and reduction of *S. aureus* [2].
Spiralin® is a defined extract generated by a patented process from the microalga *Spirulina platensis*. The extract and specifically Calcium-spirulan (Ca-SP), a sugar contained therein, has been shown to exert a broad spectrum of anti-microbial effects including anti-bacterial and anti-viral effects. For example, Ca-SP was shown to inhibit the adherence of herpes simplex virus to human keratinocytes and the subsequent cell entry, and a gel containing Ca-SP and Spiralin® prevented lip herpes exacerbation in a clinical trial with predisposed individuals [3]. The gel also appeared to be clinically effective in the treatment of molluscum contagiosum infections in children [4]. The objective of the present study was to collect first evidence on the possible effect of Spiralin® on the composition of the skin microbiome and the clinical activity in patients with active AD lesions.

Methods

In this double-blind, intraindividual, vehicle-controlled pilot study (TOMBIO-AD), n = 20 patients (female/male n = 14/6) with a mean age of 33 y (SD 11.8, range 18-57 y) with mild to moderate AD [eczema area and severity index (EASI) ≤16, body surface area (BSA) ≤10, dermatology life quality index (DLQI) ≤10], applied the active gel containing 1% Spiralin® (ilon® Hautgel AD/Skinicer® Repair Gel) or indistinguishable vehicle gel, respectively, on two AD lesions of similar size and severity for intraindividual comparison twice daily over 4 weeks with visits at baseline, weeks 1, 2, and 4. Target areas (at least 20 cm^2) were selected by the investigator and had to be positive for *S. aureus* on routine microbiological investigation at baseline. The abundance of *S. aureus* (primary endpoint) and the Shannon index (□-diversity) were calculated from the analysis of 16s rRNA gene libraries as described [5, 6] with non-lesional skin and room air samples serving as controls. Lesional disease activity was assessed by the Target Lesion Severity Score (TLSS) an adaptation of the EASI (sign scores without area involvement, ranging from 0 to 12) [7]. The size of target lesions was quantified by weighing a transparent foil (0.055 g/cm^2) precisely reflecting the lesion size and converted to area. The weighted TLSS was the product of the TLSS and the respective foil weight in g. All analyses were descriptive. No imputation of missing data was performed, and comparisons were not controlled for multiplicity. The study was conducted according to ICH-GCP guidelines, and all patients signed an informed consent form at study entry. The study was approved by the Ethical Committees responsible for the participating sites in Kiel and Hamburg.

Results

Target lesions treated with active gel and those treated with vehicle were similar in clinical activity and size at baseline (TLSS 8.6 ± 0.7 verum and 8.6 ± 0.8 vehicle; area 83.0 ± 48.1 cm^2 verum and 77.0 ± 51.5 cm^2 vehicle). All patients completed the study. One patient used systemic corticosteroids after week 1, and the clinical and microbiome data from week 2 on were considered missing. Another patient's data was considered missing at week 4 since he bathed directly prior to the visit. There was a higher decrease in the abundance of *S. aureus* in verum- than in vehicle-treated areas between baseline and week 4 (25.5% vs. 9.4%), but significance was not met. The Shannon index reflecting microbiome diversity increased in areas treated with verum over time ($p = 0.032$, Pearson correlation), but not in areas treated with vehicle. Compared to the baseline value of 1.8 (range 0.3–2.7) the Shannon index increased significantly to 2.1 (range 1.2–2.9; mean increase 16.7%) at week 4 in verum-treated areas ($p<0.01$, Wilcoxon rank-sum test), while the difference in areas receiving vehicle was not significant (Fig. 1). Changes in the Shannon index between areas treated with verum vs. those treated with vehicle were similar when patients with target lesions on the arms (n = 14) were analyzed separately as a sensitivity analysis to account for a potential influence of the

anatomical location. There was evidence for an effect of the clinical response as the mean increase of the Shannon index in response to active gel was numerically higher in lesions showing an at least 50% (26.3%) or at least 75% reduction of the TLSS (33.3%) than in all lesions.

There were several trends indicating clinical effects of the active gel, but findings were not statistically significant. The TLSS showed an approximately 10% greater reduction in verum-treated than in vehicle-treated areas at week 4. An at least 50% reduction of the TLSS was observed in 36.8% of lesions treated with verum versus 26.3% of lesions treated with vehicle. In addition, vehicle-treated areas showed no reduction in area size (77.8 cm^2 at week 4 compared to 77.0 cm^2 at baseline), while verum-treated lesion area decreased on average by 6.9 cm^2. An example of a clinical response is shown in Fig. 2. Active and vehicle gel were well tolerated and there were no serious adverse events. Local side effects rated as possibly related were noted in two patients (one case of moderate burning sensation and one case of mild pruritus).

Discussion

The results of this proof-of-concept study indicate a positive effect of a gel containing the defined microalgae extract Spiralin® on the skin microbiome in patients with active AD lesions. The reduction of *S. aureus* is in line with earlier *in vitro* findings that demonstrated strong anti-bacterial effects of Spiralin® on *S. aureus* including MRSA [8]. In contrast to topically applied antibiotics such as fusidic acid, which may reduce Shannon diversity and select for resistant *S. aureus* during treatment of AD patients [9], we did not observe evidence of a reduced microbiome diversity. Minor anti-microbial effects seen in vehicle-treated areas may be related to the 0.15% rosemary oil contained in the gel formulation [10]. Interestingly, the magnitude of the effects of the active gel on Shannon diversity in active lesions were similar to those observed with systemic anti-IL-4Ra and anti-IL-13 antibodies in patients with moderate-to-severe AD [5, 6]. Positive effects on the skin microbiome were associated with reductions in clinical disease activity scores although the differences compared to vehicle did not reach statistical significance in this relatively small study. There was some evidence for stronger microbiome effects in lesions with higher levels of clinical response. While significant improvement of AD by targeting main immune pathways has been associated with reduction of *S. aureus* [5, 6], we, therefore, speculate that the weaker clinical effects observed here occurred primarily as a consequence of microbiome changes. Of note, target lesions were treated with only 64% (verum) and 68% (vehicle) of the advised 1 g/100 cm^2 which may have impacted outcomes. The preliminary findings obtained in this study support investigation of the active gel alone or in combination with anti-inflammatory treatments in larger studies in patients with AD.

Statements

Acknowledgement

We thank the patients for their participation in the study.

Statement of Ethics

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by Ethical Committee of the Medical Faculty of the Christian-Albrechts-University Kiel - approval: D 403/20 and was also approved by the Ethical Committee of the Chamber of Physicians Hamburg – approval: MC-063/20.

All adult participants provided written informed consent to participate in this study.

Conflict of Interest Statement

KR has served as advisor for Ocean Pharma, the company that originally developed Spiralin®.

NT, JLKR, CS, TB, JH, IH, SG and SW have no conflicts of interest to declare.

Funding Sources

The study was funded by an unrestricted grant from CESRA Pharma, Baden-Baden, Germany. CESRA had no influence on the design, conduct or analysis of the study.

Author Contributions

KR designed the study, produced all study materials and analyzed and interpreted the clinical results and drafted the manuscript.

NT performed the study, collected all study data and critically reviewed the manuscript for important intellectual content.

JLKR gave important input in the interpretation of data and drafted the manuscript.

CS and TB contributed to the design of the study, produced the study materials and analysed, interpreted the clinical results and critically reviewed the manuscript for important intellectual content.

JH and IH performed the microbiome analyses, interpreted the clinical results and critically reviewed the manuscript for important intellectual content.

SG and SW interpreted the clinical results and critically reviewed the manuscript for important intellectual content.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request.

References

1. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. Lancet. 2020 Aug 1;396(10247):345-360
2. Edslev SM, Agner T, Andersen PS. Skin Microbiome in Atopic Dermatitis. Acta Derm Venereol. 2020 Jun 9;100(12):adv00164
3. Mader J, Gallo A, Schommartz T, Handke W, Nagel CH, Günther P, Brune W, Reich K. Calcium spirulan derived from Spirulina platensis inhibits herpes simplex virus 1 attachment to human keratinocytes and protects against herpes labialis. J Allergy Clin Immunol. 2016 Jan;137(1):197-203
4. Jungclaus K, Mascarenhas R, Tellechea O, Reich JLK, Reich K. Open-Label Observational Study of a Topical Formulation of Calcium Spirulan Contained in a Defined Extract of the Microalga *Spirulina platensis* in the Treatment of Children with Molluscum Contagiosum. Dermatol Res Pract. 2023 Aug 2;2023:8871299
5. Hartmann J, Moitinho-Silva L, Sander N, Harder I, Häsler R, Rodriguez E, Haufe E, Kleinheinz A, Abraham S, Heratizadeh A, Weisshaar E, Schäkel K, Handrick C, Augustin M, Wollenberg A, Staubach-Renz P, Ertner K, Sticherling M, Schwarz B, Quist S, Wiemers F, Schenck F, Wildberger J, Tittmann L, Lieb W, Schmitt J, Werfel T, Weidinger S; TREATgermany Study Group. Dupilumab but not cyclosporine treatment shifts the microbiome toward a healthy skin flora in patients with moderate-to-severe atopic dermatitis. Allergy. 2023 Aug;78(8):2290-2300
6. Sander N, Stölzl D, Fonfara M, Hartmann J, Harder I, Suhrkamp I, Jakaša I, van den Bogaard E, van Vlijmen-Willems I, Szymczak S, Rodriguez E, Gerdes S, Weidinger S. Blockade of IL-13 signaling improves skin barrier function and biology in patients with moderate to severe atopic dermatitis. Br J Dermatol. 2024 Mar 26:ljae138. doi: 10.1093/bjd/ljae138. Online ahead of print.
7. Bissonnette R, Pavel AB, Diaz A, Werth JL, Zang C, Vranic I, Purohit VS, Zielinski MA, Vlahos B, Estrada YD, Saint-Cyr Proulx E, Ports WC, Guttman-Yassky E. Crisaborole and atopic dermatitis skin biomarkers: An intrapatient randomized trial. J Allergy Clin Immunol. 2019 Nov;144(5):1274-1289
8. Pianta E, Günnewich N, Zimmermann Ch, Günther P, Petrini O, Diaz-Miyar J, Fragoso-Corti C. In Vitro Antibacterial and Antifungal Activity of an *Arthrospira platensis* (Syn.: *Spirulina platensis*) Extract. Nat. Prod. Commun. 2025. 20(1):1-6.
9. Francis NA, Ridd MJ, Thomas-Jones E, Shepherd V, Butler CC, Hood K, Huang C, Addison K, Longo M, Marwick C, Wootton M, Howe R, Roberts A, Haq MI, Madhok V, Sullivan F; CREAM team A randomised placebo-controlled trial of oral and topical antibiotics for children with clinically infected eczema in the community: the ChildRen with Eczema, Antibiotic Management (CREAM) study. Health Technol Assess. 2016 Mar;20(19):i-xxiv, 1-84
10. Jiang Y, Wu N, Fu YJ, Wang W, Luo M, Zhao CJ, Zu YG, Liu XL. Chemical composition and antimicrobial activity of the essential oil of Rosemary. Environ Toxicol Pharmacol. 2011 Jul;32(1):63-8

Figure legends

Figure 1. Shannon index reflecting a-diversity in untreated non-lesional control areas (left), target areas treated with vehicle (middle) and target areas treated with active gel (right) at baseline (red bars) and after 4 weeks of therapy (green bars). p values from Wilcoxon rank-sum test; n represents patients with valid samples (see text).

Figure 2. Example of clinical response. Target area treated with active gel (ventral right ankle) at baseline (a) and after 4 weeks of therapy (b) compared to control target area treated with vehicle (ventral left ankle; c, baseline; d, week 4). Scale bars are in centimeter.