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Barrier Repair Therapy in Atopic Eczema: Effects of Isoleucine, Rhamnosoft, Ceramides and Niacinamide Facial and Body Creams on Clinical, Itch and *Staphylococcus aureus* Skin Colonization: A Prospective Assessor-Blinded Study

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Abstract

Background: Atopic eczema (AE) is a very common chronic skin inflammatory disease of pediatric age. Skin xerosis and itch are the hallmark of the disease pointing out that skin barrier alteration is the background condition of AE. Skin barrier alteration could favour *S. aureus* colonization which in turn could be a process involved in AE flares. Due to their positive effects on skin barrier functions emollient and moisturizing compounds are considered a mainstay therapy of AE. New emollient and moisturizing facial and a body creams containing L-isoleucine, ceramides, niacinamide and rhamnosoft have been recently developed (Pro-AMP body and facial creams). The composition of these creams could act on different aspects of skin barrier defects improving skin barrier functions in AE. In particular L-isoleucine and its analogues are highly specific anti-microbial peptides (AMP) inducers in epithelial cells.

Study aim: We evaluated in a prospective assessor-blinded clinical evaluation study, the effects of pro-AMP facial and body creams on clinical evolution, itch and *S. aurues* colonization in children with mild-to-moderate AE.

Subjects and methods: A total of 45 children (24 girls and 21 boys; mean age 5 years) were enrolled after their parents' written informed consent. Treatments were applied twice daily for a 2-month period on the affected area (face, neck, upper limbs, body and lower limbs). Eczema Area Severity Index (EASI) score (face/neck and body) scoring redness, thickness scratching and lichenification was assessed using a 4-point grading severity score (from 0: absent, to 3: severe) and evaluated at baseline, month 1, and month 2. Itching was evaluated using an Analogue-Visual scale (VAS) from 0 (no itch to 10 very severe itch). Skin swabs for detection of *S. aureus* were obtained from lesional skin at baseline and at month 2.

Results: At baseline, EASI facial and body scores mean (SD), were 1.6 (0.8) and 1.9 (0.9) respectively. Itch VAS score at baseline was 6.4 (2.8). Nine (20%) subjects were positive for *S. aureus* at baseline. EASI scores significant decreased by 50% (facial) and by 52% (body) at month 1. At month 2, EASI facial, and body scores decreased by 75%, and 79%, respectively. Itch VAS score was reduced by 42% at week 4 and by 66% at week 8. All but one subjects with *S. aureus* at baseline had negative skin swabs at month 2.

Conclusion: These new Pro-AMP facial and body creams containing isoleucine, ceramides, niacinamide and rhamnosoft have shown to be effective in reducing signs and symptoms in mild-to-moderate chronic lesions of AE of the body. Treatment was also associated with an improvement on lesion skin dysbiosis.

Keywords: Emollient; Atopic eczema; Iso-leucine; *S. aureus*; Prospective study

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Introduction

Atopic eczema (AE) is a very common chronic skin inflammatory disease of pediatric age [1]. It affects 15%-20% of childhood population [2]. Skin xerosis and itch are the hallmark of the disease [3], pointing out that skin barrier alteration is the background condition of AE [4]. Skin barrier alterations such as xerosis [5], increased skin pH, alteration of innate immunity with a reduction in anti-microbial peptides production [6], could favour *S. aureus* colonization which in turn could be a process involved in AE flares [7]. *S. aureus* infection is, in fact, the most common complication of AE and it is involved in the worsening of the disease [8]. Due to their positive effects on skin barrier functions emollient and moisturizing compounds are considered a mainstay therapy of AE [9]. Emollient therapy could also have a beneficial indirect effect on normal skin micro biome [10]. New emollient and moisturizing facial and a body creams containing isoleucine 2%, ceramides 0.01%, niacinamide 1%, dimethicone 1.7% and rhamnosoft 0.2% have been recently developed (Pro-AMP facial body cream). The composition of these creams could act on different aspects of skin barrier defects improving skin barrier functions in AE. In particular L-isoleucine and its analogues are highly specific anti-microbial peptides (AMP) inducers in epithelial cells [11]. In addition rhamnosoft could interfere with the adhesion of *S. aureus* on the skin [12]. Therefore the peculiar composition of these emollient creams could be particularly effective in children with AE not only improving skin barrier but also strengthening some skin innate mechanisms like AMP production.

Study aim

We evaluated in a prospective assessor-blinded clinical evaluation study, the effects of pro-AMP facial and body creams on clinical evolution, itch and *S aureus* colonization in children with mild-to-moderate AE.

Subjects and methods

In a no-profit, two-center, prospective, assessor-blinded, trial children between the age of 6 months to 14 years with AE of the face and body were enrolled. This study was conducted in two Pediatric Clinics in Italy (Clinical Trial number: ISRCTN24922464). After obtaining institutional review board approval and parents informed consent, we studied subjects with mild-to-moderate AE. A total of 45 children (24 girls and 21 boys; mean age 5 years) participated to the trial after their parents' written informed consent. Diagnosis of AE was performed according to Hanifin and Rajka criteria [12,13]. Main exclusion criteria were severe AE, recent (i.e., <4 weeks) treatment with systemic or topical steroids, calcineurin inhibitors, or topical and systemic antibiotic drugs, or use of intranasal topical mupirocin. Study took place in two pediatric outpatient services centers in Italy between January and September 2015. For lesions on the face a cream containing isoleucine 2%, rhamnosoft (Gum2) 0.2% and ceramides 0.01% (ceramide 3 and ceramide NP) was used (Nutratopic pro-AMP facial cream, Isdin SA, Barcelona Spain). For lesions located in upper and lower limbs a cream containing isoleucine 2%, rhamnosoft (Gum 2) 0.2%, ceramides 0.01%, niacinamide 1% and dimethicone 1.7% was utilized (Nutratopic pro-AMP emollient cream, Isdin SA, Barcelona Spain). Treatments were applied twice daily, once in the morning and once in the evening, for a 8-week period on the affected areas (face, neck, upper limbs, body and lower limbs). The mean amount of products used was 18 Finger Tip Units daily (9 g). Eczema Area Severity Index (EASI) score (for face/neck, and for the body: upper limbs and lower limbs) scoring redness, thickness scratching and lichenification was assessed using a 4-point grading score (from 0: absent, to 3: severe) and evaluated at baseline, month 1, and month 2. Evaluation of EASI scores were performed in an assessor-blinded fashion. Itching was evaluated using a Visual Analogue Scale (VAS) from 0 (no itch) to 10 (very severe itch). Skin swabs for detection of *S. aureus* were obtained from at least three lesional skin sites at baseline and at month 2. Protocol-specified primary outcomes of the study were the evolution of EASI and VAS itching scores. Secondary outcome of the study was the evolution of the percentage of subjects with positive swabs for *S. aureus*. Samples were collected by a modified skin scrub technique with a cotton swab. A swab was wetted in 5 ml of Williamson-Kligman buffer at pH 7.9 containing 0.01% Triton X-100. The study was conducted in compliance with the Helsinki Declaration principles and in accordance with the International Committee for Harmonization Guidelines for Good Clinical Practice [14].

Statistical analysis

Statistical analysis was performed using Graphpad-TM (SanDiego, CA, USA) statistical software. We used the Wilcoxon paired test for the primary outcomes evaluation (evolution of ESI scores) and the VAS score. The Fisher's exact test was used for thecomparison of percentage of *S. aureus* positive subjects during the study. Continuous data are expressed as means and standard deviations (SDs). According to the study design not a formal calculation of sample size was performed. We decided to enroll at least 40 subjects.

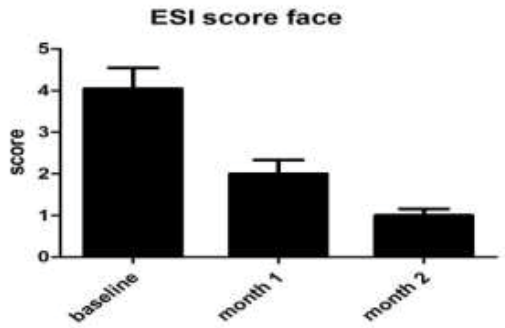
Results

Table 1 shows the demographic and clinical characteristics of the 45 enrolled subjects at baseline. All subjects concluded the study period. At baseline, ESI facial, and body (upper limbs and lower limbs) scores, mean (SD), were 4.0 (2.2), and 3.3 (2.2) respectively. Itch VAS score at baseline was 6.4 (2.8). Nine (20%) subjects were positive for *S. aureus* at baseline. In patients with positive swabs for *S. aureus* at baseline, EASI score was significantly higher (+37%) than the EASI score in the group negative for *S. aureus*, (p=0.03), confirming that the presence of these bacteria is linked to a worse clinical presentation. In all the treated subjects EASI scores significant decreased by 50% (facial) and by 52% (body) at month 1. At month 2, EASI facial and body scores decreased by 75%, and 79%, respectively **(Figure 1).** Itch VAS score was reduced by 42% at month 1 and by 66% at month 2 **(Figure 2).** All but one subjects with *S. aureus* at baseline had negative skin swabs at month 2 (p=0.002; Fisher exact test).

Discussion

The skin barrier plays a vital role for the organism, preventing

a)



b)

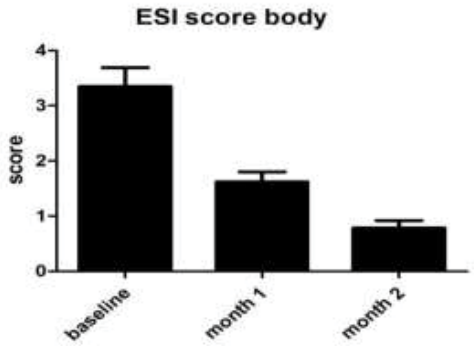


Figure 1 Evolution of Eczema Severity Index (ESI) of face (a) and body (b) at baseline and after 1 and 2 months of treatment. Baseline vs. month 1: p=0.0002; baseline vs. month 2: p=0.0001; Wilcoxon test.

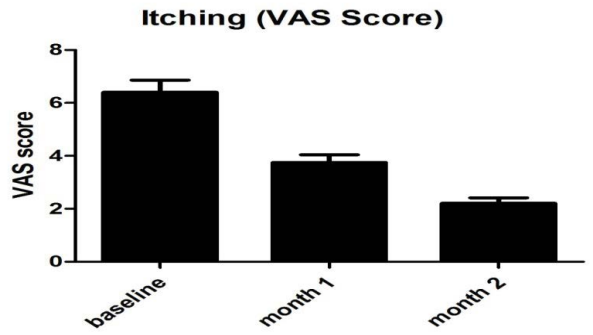


Figure 2 Evolution of Itch VAS score from baseline to month 1 and 2. Baseline vs. month 1: p=0.0003; baseline vs. month 2: p=0.0001; Wilcoxon test.

Table 1 Subjects' characteristics at baseline.

N	45
Male/female, n (%)	21 (47%)/ 24 (53%)
Age (years) mean (SD)	05 (3.7)
History of atopic eczema, years, mean (SD)	03 (2.6)
History of respiratory allergies (rhinitis/asthma) Yes No	 04 (10%) 41 (90%)
EASI score at baseline Face Body	 1.6 (0.8) 1.9 (0.9)

percutaneous entry of patogens into the body, modulating thermoregulation and maintaining a proper hydration of the skin [15]. An alteration of skin barrier functions has been documented in atopic eczema, both in affected areas and in normal appearing skin [16]. In particular xerosis is a hallmark of AE and affects both lesional skin and also unaffected skin regions [17]. In addition a relevant function of skin barrier is linked to the innate immunity mechanisms [18]. Keratinocytes produce anti-microbial peptides (AMP) and the skin acid pH offer additional protection against pathogens [19]. For example keratinocytes are able to produce and storage in the lamellar bodies cathelicidin [20]. In subjects with atopic eczema a defective production of AMP has been demonstrated [21]. Atopic eczema skin is characterized by a dysbiosis status in which the presence of normal "protective" bacterial strains like *S. epidermidis* could be replaced by an abnormal proliferation of *S. aureus* [22]. *S aureus* colonization in AE subjects is involved in the worsening of the disease and AE exacerbation are associated with a decrease in microbial diversity (dysbiosis) on lesional skin [23]. *S. aureus* is able to secrete exotoxins with super-antigenic properties [24]. On this respect, systemic or topical antibiotic therapies could be an important component of AE treatment when there is a super-infection. However diffuse use of antibiotics could facilitate the spread of methicillin-resistant *S aureus* (MRSA) strains which in turn could be a therapeutic challenge: a recent meta-analysis shows that there is a clear association between exposure to antibiotics and MRSA isolations [25]. In addition in subject with AE but with not *S. aureus* super-infection a recent meta-analysis [26] evaluating different anti-staphylococcal interventions has shown that none of the studies showed any clinical benefit. Emollient and moisturizing products with the aim to improve skin barrier properties of AE subjects are now considered a fundamental approach in the strategic treatment of this skin condition [27]. Improvement of skin barrier functions (water content, normalization of skin pH) can "per se" improve also the innate immune defenses of the skin. Recently, Seite et al. [9] have demonstrated that the use of an emollient is associated with an improvement of skin microbiome in AE subjects. However there are not so far topical emollient or moisturizing products with specific components which could improve in a direct manner the innate defensive mechanisms of the skin and in particular the production of AMP. In the present study we evaluate the effect of two topical products containing rhamnosoft, isoleucine, niacinamide and ceramides. Topical ceramides could restore the altered skin barrier in AE [28,29]. Rhamnosoft is a rhamnose-rich polysaccharide with high affinity tokeratinocyte receptors sharing anti-inflammatory and antibacterial adhesion properties [30]. In addition rhamnosoft could interfere with the adhesion of *S. aureus* on the skin. Topical isoleucine has shown to stimulate a skin level production of AMP [31]. Isoleucine is also able to potentiate the functional activities of beta defensin, increasing its chemo-attractant activity. Therefore the use of topical anti-inflammatory, emollient and moisturizing products containing

also compounds which could improve the innate immunologic system of the skin such as isoleucine could be a further step in the rational topical treatment approach in AE. In this study we have shown that use of rhamnosoft, ceramides, niacinamide and isoleucine facial and body creams improve significantly signs and symptoms in children with mild-to-moderate AE. These data confirm the results we have observed in a multicenter, controlled, comparative study carried out in 105 children with atopic eczema of the face. In addition we have observed that after two months of application of the creams there is an improvement of the dysbiosis status observed at baseline in roughly 1/3 of this sample. Some limitations should be taken in account in evaluating the results of the present study. First this was not a randomized double blind trial. In order to increase the internal validity of our trial we adopted an assessor-blinded clinical evaluation approach regarding the primary outcome i.e., evolution of ESI score. A second aspect is related to the fact that we enrolled mild to moderate AE subjects therefore the results of our trial could be not applied in AE subject with acute flares. The pathogenetic role of *S aureus* colonization seems more correlated with severe form of AE in comparison with mild to moderate cases. However in the subset of subjects with positive *S aureus* we found that baseline ESI score was significantly greater than the ESI score of subjects with negative *S aureus* swabs suggesting that also in mild to moderate cases the presence of *S. aureus* could be linked with a more severe clinical manifestation of the eczema. The application of the study creams was associated with an improvement of this dysbiosis status in this subset of subjects. These data suggest that also in mild to moderate AE the normalization of skin microbioma could have positive effect in the clinical outcome.

Conclusion

These new Pro-AMP facial and body creams containing isoleucine, niacinamide, ceramides and rhamnosoft have shown to be effective in reducing signs and symptoms (itch) in mild-to-moderate chronic lesions of AE of the body. Treatment was also associated with an improvement on lesion skin dysbiosis.

References

1 Williams H, Robertson C, Alistair S, Aït-Khaled N, Gabriel A, et al. (1999) Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. Journal of allergy and clinical immunology 103: 125-138.

2 Eichenfields LF (2004) Consensus guidelines in diagnosis and treatment of atopic dermatitis. Allergy 59: 86-92.

3 Eberlein-Koè Nig B, Schaè Fer T, Huss-Marp J, Darsow U, Ring J, et al. (2000) Skin surface pH, stratum corneum hydration, trans-epidermal water loss and skin roughness related to atopic eczema and skin dryness in a population of primary school children: clinical report. Acta Dermatology-Venerology 80: 188-191.

4 Boguniewicz M, Leung DY (2011) Atopic dermatitis: a disease of altered skin barrier and immune dysregulation. Immunological reviews 242: 233-246.

5 Yoshiike T, Aikawa Y, Sindhvananda J, Suto H, Nishimura K, et al. (1993) Skin barrier defect in atopic dermatitis: increased permeability of the stratum corneum using dimethyl sulfoxide and theophylline. Journal of dermatological science 5: 92-96.

6 Ong PY, Ohtake T, Brandt C, Strickland I, Boguniewicz M, et al. (2002) Endogenous antimicrobial peptides and skin infections in atopic dermatitis. New England Journal of Medicine 347: 1151-1160.

7 Abeck D, Mempel M (1998) Staphylococcus aureus colonization in atopic dermatitis and its therapeutic implications. British Journal of Dermatology-Supplement 139: 13-16.

8 Cork MJ, Simon D (2009) Skin barrier breakdown: a renaissance in emollient therapy. British Journal of Nursing 18: 872-877.

9 Flores GE, Seitè S, Henley J (2014) Microbiome of affected and unaffected skin patients with atopic dermatitis before and after emollient treatment. J Drugs Dermatol 13: 1365-1372.

10 Zasloff M (2002) Antimicrobial peptides of multicellular organisms nature. Nature weekly jour 415: 389-395.

11 Faury G (2000) Receptors and aging: Structural selectivity of the rhamnose-receptor on fibroblasts as shown by Ca^{2+}-mobilization and gene-expression profiles. Disertační práce. p: 50.

12 Hanifin JM, Rajka G (1980) Diagnostic features ofatopic dermatitis. Acta Derm Venereol (Stockh) 92: 44-47.

13 ICH (2014) International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) adopts Consolidated Guideline on Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use. Int Dig Health Legis 48: 231-234.

14 Proksch E, Johanna BM, Jens-Michael J (2008) The skin: an indispensable barrier. Experimental dermatology 17: 1063-1072.

15 Elias Peter M, Matthias S (2009) Abnormal skin barrier in the etiopathogenesis of atopic dermatitis. Current allergy and asthma reports 9: 265-272.

16 Proksch E, Folster-Holst R, Jensen JM (2006) Skin barrier function, epidermal proliferation and differentiation in eczema. J Dermatol Sci 43: 159-169.

17 De Benedetto A, Agnihothri R, McGirt LY, Bankova LG, Beck LA (2009) Atopic Dermatitis: A Disease Caused by Innate Immune Defects & quest. Journal of Investigative Dermatology 129: 14-30.

18 Frohm M, Agerberth B, Ahangari G, Stâhle-Bäckdahl M, Lidén S, et al. (1997) The expression of the gene coding for the antibacterial peptide LL-37 is induced in human keratinocytes during inflammatory disorders. Journal of Biological Chemistry 272: 15258-15263.

19 Braff MH, Anna DN, Richard GL (2005) Keratinocytes store the antimicrobial peptide cathelicidin in lamellar bodies. Journal of investigative dermatology 124: 394-400.

20 Rieg S (2005) Deficiency of dermcidin-derived antimicrobial peptides in sweat of patients with atopic dermatitis correlates with an impaired innate defense of human skin in vivo. The Journal of Immunology 174: 8003-8010.

21 Sabine Gisela P, Johannes R (2010) What's new in atopic eczema?. Expert opinion on emerging drugs 15: 249-267.

22 Marie-Anne M (1994) Atopic dermatitis: triggering factors. Journal of the American Academy of Dermatology 31: 467-473.

23 Poul S (1996) Staphylococcal enterotoxin B applied on intact normal and intact atopic skin induces dermatitis. Archives of dermatology 132: 27-33.

24 Tacconelli E, De Angelis G, Cataldo MA, Pozzi E, Cauda R (2008) Does antibiotic exposure increase the risk of methicillin-resistant Staphylococcus aureus (MRSA) isolation? A systematic review and meta-analysis. Journal of Antimicrobial Chemotherapy 61: 26-38.

25 Bath-Hextall FJ, Birnie AJ, Ravenscroft JC, Williams HC (2010) Interventions to reduce Staphylococcus aureus in the management of atopic eczema: an updated Cochrane review. British Journal of Dermatology 163: 12-26.

26 Grimalt R, Mengeaud V, Cambazard F (2007) The steroid-sparing effect of an emollient therapy in infants with atopic dermatitis: a randomized controlled study. Dermatology 214: 61-67.

27 Chamlin SL, Kao J, Frieden IJ, Sheu MY, Fowler AJ, et al. (2002) Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: changes in barrier function provide a sensitive indicator of disease activity. Journal of the American Academy of Dermatology 47: 198-208.

28 Andres E, Molinari J, Peterszegi G (2006) Pharmacological properties of rhamnose-rich polysaccharides, potential interest in agedependent alterations of connectives tissues. Pathol Biol (Paris) 54: 420-425.

29 Sherman H, Chapnik N, Froy Albuminand O (2006) amino acids upregulate the expressionof human beta-defensin 1. Mol Immunol 43: 1617-1623.

30 Tyrrell C, De Cecco M, Reynolds NL (2010) Isoleucine/leucine 2 is essential forchemoattractant activity of beta-defensinDefb 14 through chemokine receptor 6. MolImmunol 47: 1378-1382.

31 Marseglia A (2014) Efficacy of a rhamnosoft, ceramides, and L-isoleucine cream in atopic eczema of the face: a randomized controlled trial. Pediatric Allergy and Immunology 25: 271-275.