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Efficacy, tolerability and acceptability of topical regimens containing the prebiotic Biolin in children suffering from atopic dermatitis.

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Summary

Prebiotics have the potential to correct skin dysbiosis and contribute to the improvement of atopic dermatitis (AD) when incorporated in topical moisturizers and emollients. Biolin is a combination of two prebiotics, alpha-glucan-oligosaccaride and inulin. This is the first study to test Biolin containing creams in AD in children. The study is aimed at assessing the efficacy, tolerability, acceptability and effects on quality of life of three Biolin containing topical creams (face cream, body wash cream and moisturizing body cream) in children with AD. This is single center, open label study, carried for 8 weeks in parallel subgroups of children aged 0-3 years with mild to moderate AD (SCORAD<35). Face and body wash creams were tested for 56 consecutive days in a subgroup of 30 subjects and the moisturizing body cream in the other 30 subjects' subgroup. SCORAD indexes, xerosis, erythema and edema were assessed at the 4 study visits. Parents' assessments were carried at 14, 28 and 56 days. SCORAD indexes significantly decreased for all creams at t28 and t56; average decrease ranged from 57.7% to 58.3%. Xerosis reductions were statistically significant for all creams at t56; xerosis improved in 96.6% to 100% of children. No erythema or edema emerged in children without these signs at baseline. Averages of parameters assessed by parents (pruritus, dryness, skin softness, quality of life and creams characteristics) were 8 (out of 10) or higher at the end of the study. The Biolin containing creams tested were beneficial and well tolerated in children aged 0-3 years with mild to moderate AD. The regimens were well accepted by parents and judged to improve both clinical manifestations and quality of life.

Key words

Atopic dermatitis, children, moisturizer, dysbiosis, prebiotics.

Atopic dermatitis (AD) is a chronically recurrent inflammatory skin condition (4) affecting 10-20% of children (21). It is characterized by reduced skin hydration, erythema, swelling, oozing and crusting papules and vesicles, scaling, lichenification and pruritus. Complications consist of secondary bacterial infection mainly due to *S. aureus*, esthetic impairment, decreased quality of life and caregivers'distress.

Most patients with AD present elevated levels of circulating immunoglobulin E and usually have another atopic disorder, e.g. allergic rhinitis, asthma, or food allergy (17).

Hypotheses on AD etiology include epidermal barrier defects, as well as immune dysregulation of both the innate and adaptive immune systems, with special relevance to higher predisposition in the case of loss of function mutations in FLG, the gene encoding the skin barrier protein filaggrin (2, 15).

There is increasing evidence that AD is also correlated with skin microbiota dysbiosis without an invading pathogen (13, 19). Dysbiosis may be defined as a disruption of the normal microbiological environment that may lead to infection and has been described to result from a combined state of skin barrier impairment and immune system depression (6).

During AD flares, an increase in *S. aureus* colonization has been observed and disease severity has been correlated to decreased bacterial diversity (6).

Small family size, high socioeconomic and educational levels (regardless of ethnicity), movement from rural to urban environment and increased use of antibiotics are risk factors to AD (23).

Its negative impact on patients' and their relatives' quality of life has been extensively described (14, 16), as well as its implications for families, healthcare providers and societies (20).

AD management approaches focus primarily on reducing inflammation and symptomatically relieving pruritus with topical pharmacological treatment including corticosteroids, calcineurin inhibitors, antimicrobials and antiseptics, antihistamines and coal tar derivatives (7).

Moisturizing topical treatment remains the basic treatment for AD (18) due to effects of restoring the skin barrier function. Its use is recommended regardless of disease stage and seriousness.

Skin hydration is widely accepted as important in maintenance therapy (11, 24). It is however recognized that moisturizing and emollient formulations should undergo adequate clinical assessments so that their use in AD becomes more evidence based (5, 8).

There is increasing evidence that modulation of the skin microbiome through the administration of prebiotics promotes a balanced resident microbiome, therefore reducing the potential for skin infection and inflammation (1, 22). The direct application of cosmetic formulations containing prebiotics can increase the selective growth and activity of beneficial skin microbiota (1).

Preserving the bacteriological diversity seems to be correlated with good health status through immune system modulation. Diversity of cutaneous microbiota has been described to decrease inflammation (10).

Saprophytic microorganisms' growth helps skin lesions recovery, which is the basis for expecting an adjunctive benefit of its regular use in AD.

Along with cream intrinsic properties, acceptability and patients' preference remain relevant influencers of topical treatment outcomes (12).

Biolin is a combination of two prebiotics, alpha-glucan-oligosaccaride and inulin; it boosts the growth of saprophytic flora species (mainly *M. kristinae*) in detriment of the undesired *S. aureus*, *C. albicans* and *M. furfur* (3). Biolin is a component of a cosmetic baby care line marketed in European countries with observed beneficial effects in diaper rash prevention (6).

The objective of this study was to evaluate the efficacy in helping to reduce AD related skin dryness and itching sensation, tolerability, acceptability and effects on quality of life of three creams containing Biolin (face cream, body wash cream and moisturizing body cream) in children aged 3 or less. It is hypothesized that their use is beneficial in the studied population.

Methods

Subjects. This study involved 60 subjects, aged 0-3 years (3-36 months old), with mild to moderate atopic dermatitis assessed as SCORAD index < 35. The average age was 20 months (SD±12) and 60% were males.

To be enrolled, participants had to be in good general health state and could not suffer from any psychological disease.

Parents had to agree on not applying other cosmetic creams and not altering any other aspects of daily routine.

Children undergoing cortisone treatments could continue such therapy; their parents had to

agree on communicating the applied dosage of cortisone. Written informed consent from parents was obtained before enrollment. An Institutional Review Board reviewed and approved the study protocol; the study was conducted under the guidelines described in the Declaration of Helsinki.

Cream description. The creams tested contained Biolin (alpha-glucan-oligosaccaride and inulin) as well as several emollient, humectant, barrier repair and preservative ingredients. The qualitative compositions of each cream are listed in table 1.

TABLE 1: Qualitative compositions of face, body wash and moisturizing body creams.

Face cream	Body wash cream	Moisturizing body cream
Aqua (Water) Glycerin Ethylhexyl Palmitate Coco-Caprylate *Helianthus annuus* seed oil Behenyl alcohol Candelilla/Jojoba/Rice Bran Polyglyceryl-3 Esters Glyceryl Stearate Caprylic/Capric Triglyceride Phenethyl Alcohol Cetearyl Alcohol Sodium Stearoyl Lactylate Sodium Polyacrylate *Calendula officinalis* Flower Extract Inulin Xanthan Gum Parfum (Fragrance) Disodium EDTA Sodium Lauroyl Lactylate *Chamomilla recutita* Flower Extract Ethylhexylglycerin Alpha-Glucan oligosaccharide Citric Acid Lecithin *Linum alpinum* Flower/Leaf/Stem Extract Ceramide 3 Ceramide 6 II Phytosphingosine Cholesterol Tocopherol Ascorbyl Palmitate Carbomer Ceramide 1	Aqua (Water) Sodium Lauroyl Sarcosinate Glycerin *Oryza sativa* Bran Oil Cocamidopropyl Betaine Sodium Lauroyl Glutamate Acrylates/C10-30 Alkyl Acrylate Crosspolymer Phenoxyethanol Caprylic/capric Triglyceride Inulin Parfum (Fragrance) Sodium Hydroxyde Potassium Olivoyl Hydrolyzed Oat Protein Sodium Lauroyl OAT Amino Acids Alpha-glucan oligosaccaride Lecithin Ethylhexylglycerin Tocopheryl Acetate Tocopherol *Linum alpinum* Flower/Leaf/Stem extract Ascorbyl Palmitate Citric Acid	Aqua (Water) Ethylhexyl Palmitate Coco-Caprylate Glycerin Glyceryl Stearate *Butyrospermum parkii* (Shea Butter) Caprylic/Capric Triglyceride Candelilla/Jojoba/Rice Bran Polyglyceryl-3 Esters *Helianthus annuus* Seed Oil Cetearyl Alcohol Phenethyl Alcohol Sodium Stearoyl Lactylate Magnesium Aluminum Silicate Hydroxyethylcellulose Inulin Parfum (Fragrance) *Calendula officinalis* Flower Extract Sodium Polyacrylate Ethylhexylglycerin Disodium EDTA *Chamomilla recutita* Flower Extract Citric Acid Alpha-Glucan oligosaccharide Bisabolol Lecithin *Linum alpinum* Flower/Leaf/Stem Extract Tocopherol Ascorbyl Palmitate *Zingiber officinale* (Ginger) Root Extract

Methods and assessments

This was a single center, open label study. Data was collected from October to December 2014. The tests were performed and monitored by a pediatrician from Clinica Pediatrica De Marchi and two dermatologists from the Vittore Buzzi - Milan Children's Hospital. The group was divided into two subgroups of 30 children each. The face and body wash creams were tested in one of the subgroups and the moisturizing body cream was tested in the other subgroup.

A form containing instructions on how to apply the tested creams was provided to parents. The face cream has been applied on face twice daily. The moisturizing body cream has been applied on body also twice daily. The body wash cream has been applied on body and rinsed off once daily. The three tests were performed for 56 consecutive days.

Clinical evaluation

At the 4 study visits (baseline [t0], 14 days [t14], 28 days [t28], 56 days [t56]), the clinical evaluator assessed: 1) the SCORAD index 2) skin xerosis 3) skin tolerability (erythema and edema). The scoring systems applied are detailed in tables 2 (xerosis) and 3 (erythema and edema).

TABLE 2:
Xerosis scoring system.

Non-evident phenomenon	1
Slight evident phenomenon	2
Fairly evident phenomenon	3
Evident phenomenon	4
Very evident phenomenon	5

TABLE 3: Tolerability (erythema and edema) scoring systems.

Tolerability (skin alterations)			
Erythema		**Edema**	
No Erythema	0	No Edema	0
Slight Erythema (hardly visible)	1	Very slight Edema (hardly visible)	1
Clearly visible Erythema	2	Slight Edema	2
Moderate Erythema	3	Moderate Edema (about 1 mm raised skin)	3
Serious Erythema (dark red with possible formation of light scars)	4	Strong Edema (extended swelling even beyond the application area)	4

TABLE 4: SCORAD indexes at baseline for the three creams tested (n = 60).			
	Face cream	Body wash cream	Moisturizing body cream
Average (SD)	16.9 (10.4)	16.5 (10.3)	16.9 (9.1)
Min	3	3	4
Q1	6	6	8
Median	20	18	17
Q3	26	26	26
Max	30	30	30

Parents' evaluation

At t14, t28 and t56, parents' opinions were collected through a 10 points Visual Analogue Scale (VAS) (0 – minimum value to 10 – maximum value). The inquired subjects rated the extent to which the child's pruritus sensation, dryness, skin softness and quality of life were improved.

They were also asked to rate the creams' texture (face and body moisturizing creams only), fragrance and overall likeability using the same VAS.

Statistical analysis

The statistical analysis of the SCORAD index variation has been performed using Student «t» test. The average values were calculated for each period. The threshold of acceptability has been fixed at 5%. The statistical analysis of xerosis variation has been performed using the Friedman test (nonparametric data). The average values were calculated for each period. The test was considered significant when the average differences were higher than the threshold value (confidence interval 95%). Measures of location and dispersion were determined for the ratings provided in the parents' evaluation section. Per protocol analysis were performed.

Population

The population disease severity at baseline is depicted in table 4. One subject discontinued the face cream application due to an excessive fragrance intensity perception and was not included in the face cream per protocol analysis. All other subjects completed the study.

Results

In all visits the three creams showed improvements in SCORAD indexes; the latter were statistically significant ($p<0.05$) at t28 and t56 (Figure 1) Although consistent, decreases at t14 were not tatistically significant. At the end of the study, SCORAD improvements translated into reductions of 57- 58%.

Xerosis reduction was marked and statistically significant ($p<0.05$) for all creams at t56.

The percentage of subjects achieving a statistically significant reduction in xerosis at t56 was 90.0%, 93.0% and 97.0% for the face cream, the body wash cream and the moisturizing body cream respectively, as depicted in Figure 2.

At previous visits, the percentage of subjects where a reduction in xerosis was noticed varied from 34-50% (t14) to 70-76% (t28) but none reached statistically significance.

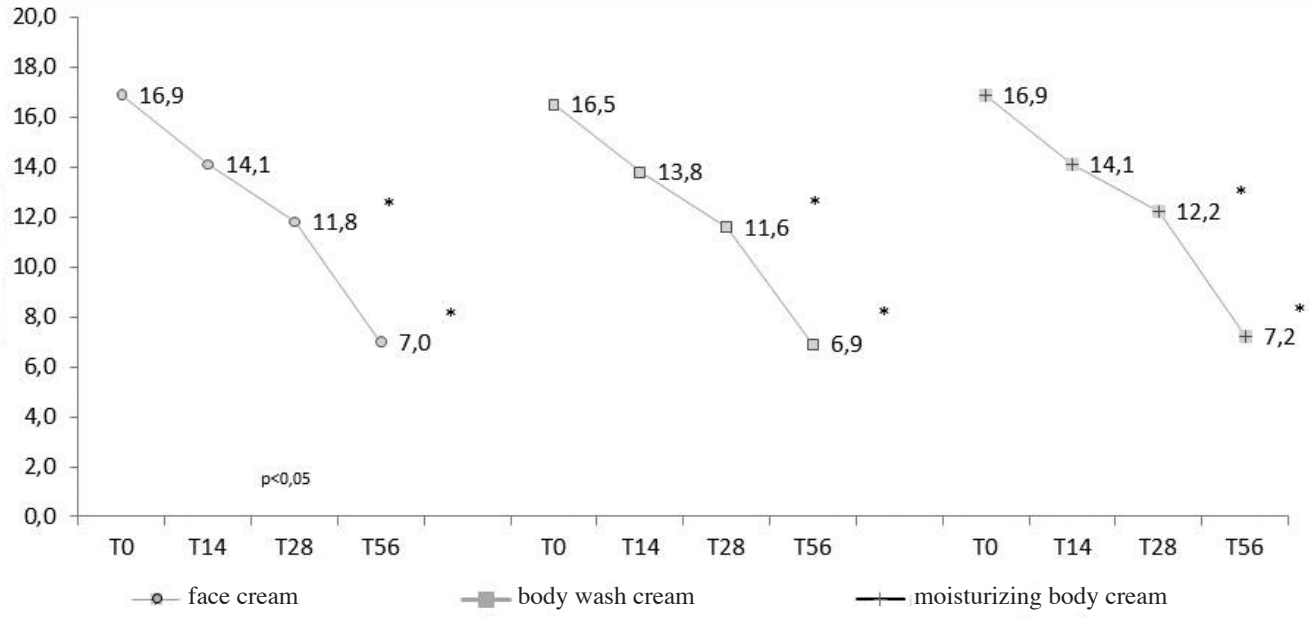

Fig. 1: Average SCORAD indexes evolution.

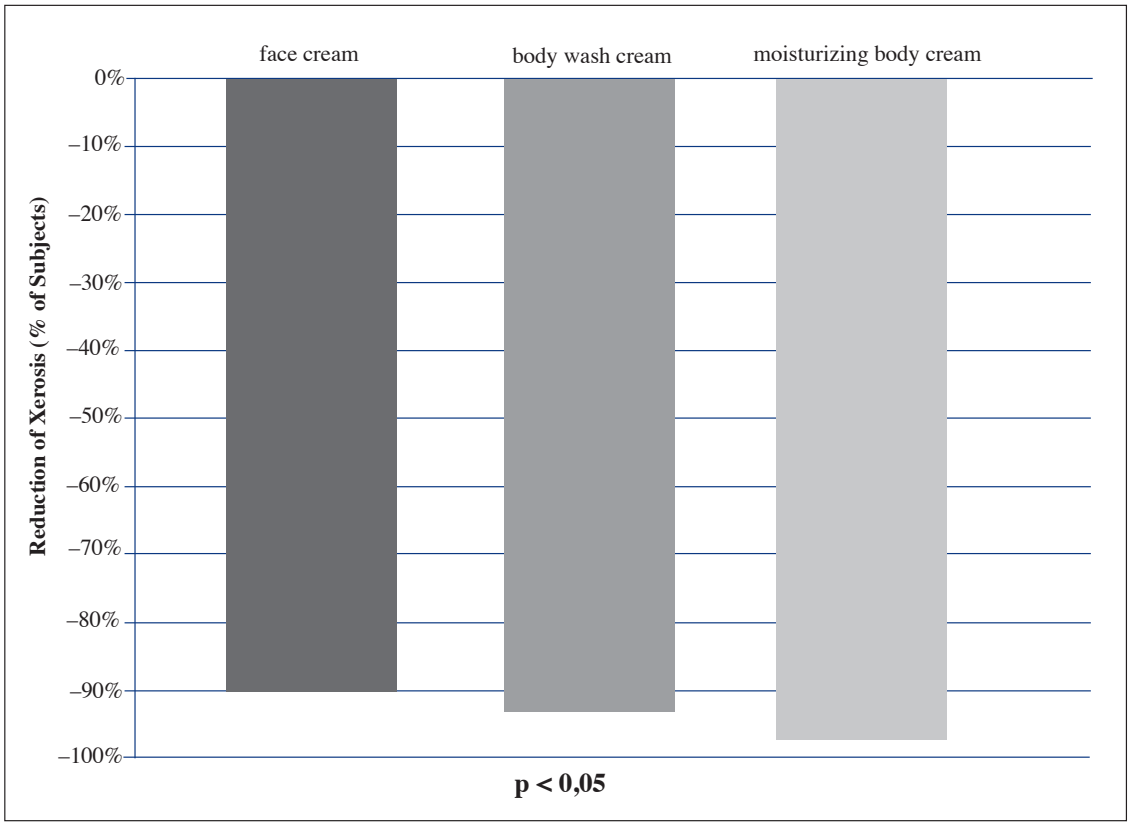

Fig. 2: Xerosis: % of subjects experiencing reduction at t56.

TABLE 5: Tolerability (erythema and edema): summary of baseline and t56 outcomes (n=60).

	Erythema			*Edema*		
	Face Cream	Body Wash Cream	Moisturizing Body Cream	Face Cream	Body Wash Cream	Moisturizing Body Cream
Nº of subjects presenting at t0	19	17	17	10	9	11
of which not improved at t56	3	0	0	3	0	0
% of reduction at t56	71,9	85,2	96,4	76,9	81,8	92,3
Nº of subjects presenting at t56	6	3	0	3	2	1
Nº of subjects presenting de novo at t56	0	0	0	0	0	0

Tolerability

Amongst subjects who did not present erythema or edema at baseline, no alterations were noticed in any of the settings.

In the face cream arm, three subjects with initial erythema and edema did not show improvements in any of the follow-up visits. In the body wash and moisturizing body creams all subjects with initial erythema and/or edema improved at t56 vs t0. At t56, average erythema reductions were 71.9% (face cream), 85.2% (body wash cream) and 96.4% (moisturizing body cream). At t56, average edema reductions were 76.9% (face cream), 81.8% (body wash cream) and 92.3% (moisturizing body cream). These and other tolerability outcomes are summarized in Table 5.

Parents' evaluation

The averages of all variables assessed in the self-evaluation section were 7 or higher at t14 and all averages were 8 or higher at t56.

Figures 3 to 5 provide details on the parents' evaluation ratings for each variable at t56.

Cortisone treatment

Amongst subjects in face and body wash creams testing, two were on cortisone treatment, reporting its use both on face and body. Dosages ("one fingertip" and "two fingertip" units) and number of applications per day (once daily) remained unchanged during the protocol duration.

In the moisturizing cream testing group, three subjects were on cortisone treatment, once daily application. Two of them were on "one fingertip" unit and one was on "two fingertip" units. The latest decreased the dosage to "one fingertip" from t28 to t56. No decreases in the number of daily applications were registered.

Discussion

This open-label clinical trial found that the individual use of the three Biolin containing creams was well tolerated and effective in improving disease severity and quality of life in pediatric patients with mild to moderate AD.

As hypothesized, their use was beneficial to the studied population. After 8 weeks of daily use

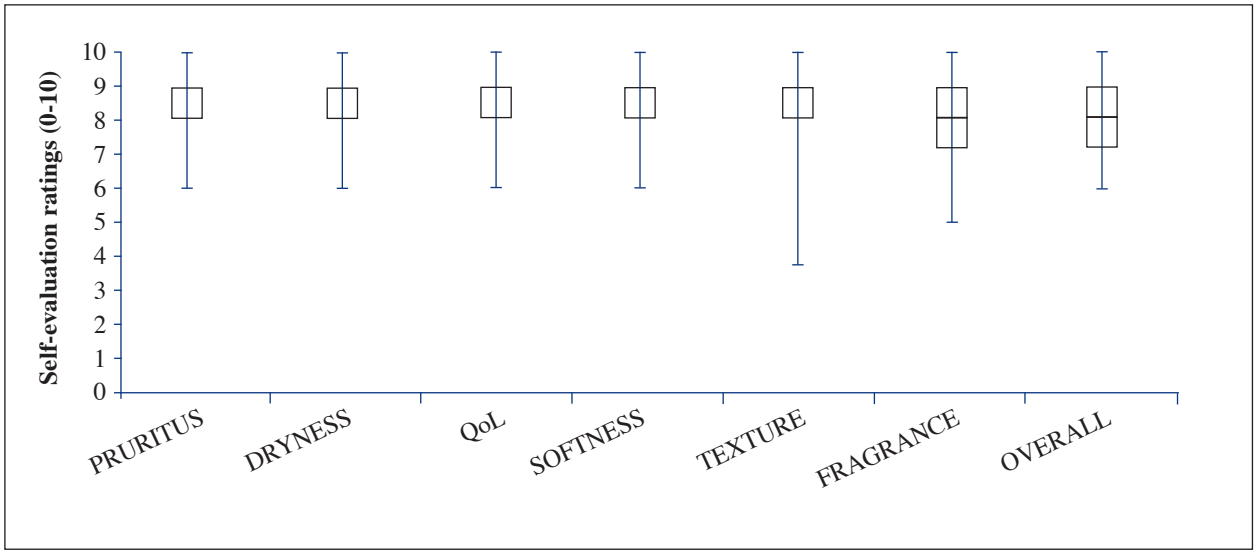

Fig. 3: Face cream parents' evaluation ratings: measures of location and dispersion at t56.
QoL- Quality of Life

SCORAD indexes and xerosis were significantly and markedly reduced supporting the creams adequacy as adjunctive maintenance regimen in AD.

No subjects free of erythema and edema at baseline developed these signs during the study; the two measures of tolerability even improved in most studied subjects. Only one subject discontinued the regimen in the face cream arm, due to an excessive fragrance intensity perception but remained in the body wash cream test.

Skin care in atopic infants is time spending and demands high levels of motivation and discipline from parents. Rigorous adherence to prescribed regimens and long-term hydrating in maintenance therapy are key in achieving good results. Being judged by caregivers as beneficial in quality of life and symptom reduction as well as

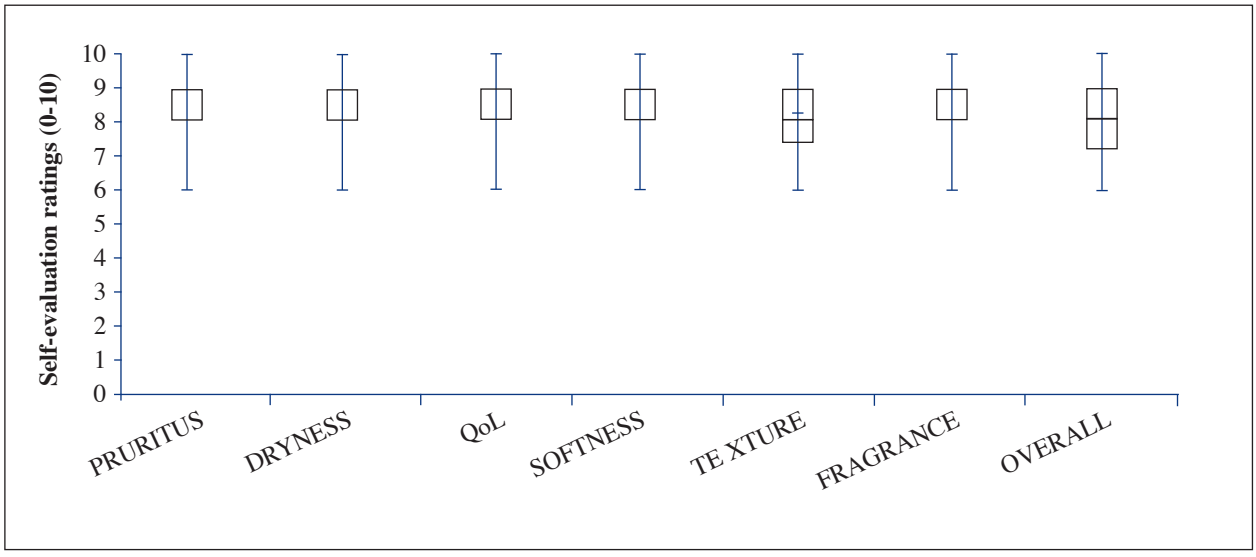

Fig. 4: Body wash cream parents' evaluation ratings: measures of location and dispersion at t56.
QoL- Quality of Life,

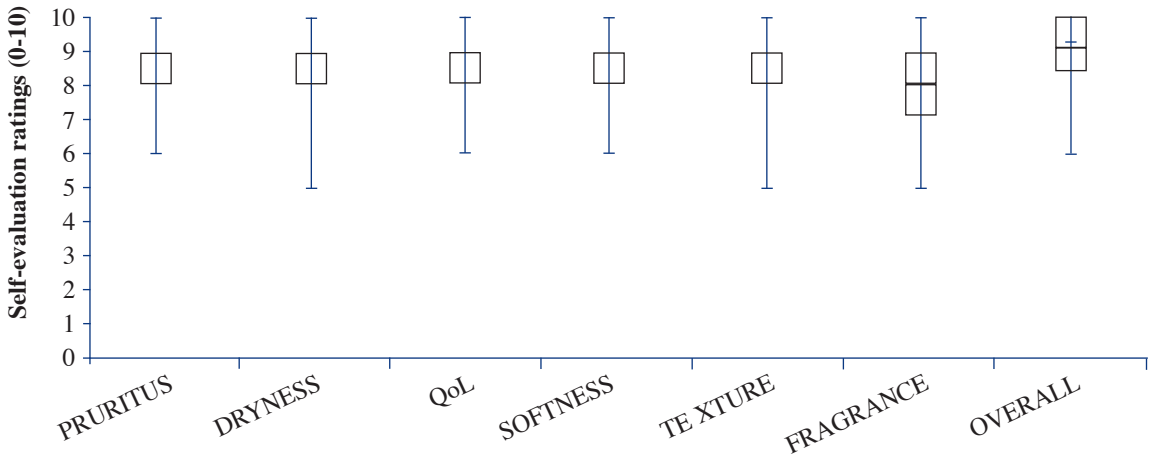

Fig. 5: Moisturizing body cream parents' evaluation ratings: measures of location and dispersion at t56.
QoL- Quality of Life

cosmetically convenient makes long term adherence more likely. The tolerability profile of the three creams tested was favorable. Atopic skins are usually nonspecifically reactive to creams and it is estimated that allergic contact dermatitis to emollients affects about 2.5% of children who suffer from atopic dermatitis (12, 20).

Patient perceived improvements in atopic dermatitis correlate with health related quality of life (14, 20), which is consistent with findings of the present study; perceived quality of life scored in average 7.5 or higher out of 10 at the end of the study.

The small number of subjects who were under cortisone treatment at baseline does not allow for conclusions to be drawn concerning the potential of the tested regimens to decrease the use of topical corticosteroids.

The tested creams contain ingredients with calming effects possibly acting synergistically with Biolin and contributing to a decrease in superficial inflammation (linum, calendula, chamomilla and ginger root extracts) as well as lipid layer repair properties (ceramides 1, 3 and 6) and emollients (including shea butter, helianthus and oryza sativa oils).

As limitations of the present study we point out the small sample size, the lack of information concerning moisturizing creams applied prior to the tests and finally the absence of compliance controls.

As future developments of Biolin research in AD we suggest the implementation of randomized clinical trials, carried in larger populations. These future studies would benefit from the use of standardized measurements of the stratum corneum hydration or of transepidermal water loss.

Carrying microbiological tests capable of establishing a correlation between microflora modulation/dysbiosis correction and AD improvement would be advisable as well.

In conclusions the Biolin containing creams tested in this study (face cream, body wash cream and moisturizing body cream) improved mild to moderate atopic dermatitis (SCORAD<35) in 8 weeks regimens and were well tolerated by children below 3 years of age. The regimens were well accepted by parents and judged to improve both the clinical manifestations and the subjects' quality of life. Further studies are recommended to definitely establish Biolin contribution to AD improvement via dysbiosis correction.

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