

Communication

New cosmetic formulation for treatment of mild to moderate infantile atopic dermatitis

Raúl de Lucas ¹, Cristina García Millán ², Azahara Pérez-Davó ³, Esther Moreno ⁴ and Pedro Redondo ⁴

¹ Department of Dermatology, Hospital Universitario La Paz, Madrid, Spain
² Dermatology Group Pedro Jaén, Madrid, Spain
³ Medical Affairs Department, Cantabria labs, Madrid, Spain
⁴ Department of Dermatology, Clínica Universitaria de Navarra

Abstract: Atopic dermatitis (AD) is a chronic cutaneous inflammatory disorder, characterized by skin barrier disruption. Dermacare is a new cosmetic formulation which enhances moisturization, reinforces and repairs the skin barrier and prevents cutaneous microbiota imbalance. To demonstrate its safety and efficacy a prospective, open-label and multicenter study was carried out on patients diagnosed with mild to moderate AD. Transepidermal water loss (TEWL), clinical severity, Desquamation Index, Patient/Investigator Global Assessments, quality of life index and tolerance were assessed. Adverse events were recorded. Daily application of the new treatment was well tolerated, and adverse events were absent. After 14 days, TEWL showed a 36.7% significant decrease ($p=0.035$). At the end of the 28-day Dermacare treatment, the Desquamation Index showed a reduction in 70% of patients; Eczema Area and Severity Index were reduced by 70.4% ($p=0.002$); and skin irritation showed a significant reduction ($p=0.024$). Likewise, Patient and Investigator Global Assessments reported a significant improvement in conditions and an overall global worsening when patients restarted their normal treatment. Parent's Index of Quality of Life Index significantly increased by 36.4% ($p<0.05$) with Dermacare. In conclusion, Dermacare's regular use helped reduce the risk of relapse and extend the steroid-free treatment periods.

Keywords: atopic, dermatitis, emollient, moisturizer, epidermal barrier, filaggrin

1. Introduction

Atopic dermatitis (AD) is a multifactorial chronic inflammatory skin disease characterized by a decreased skin barrier function that is caused by multiple factors, such as: environmental and temperature agents, environmental allergens, exogenous irritants, infections, and psychological stress; likewise immune dysregulation, defects in terminal epithelial differentiation such as lack of filaggrin (FLG), deficiency of antimicrobial peptides (AMPs), altered composition of stratum corneum intercellular lipids, and altered skin microbiome are implicated factors in pathogenesis of AD [1].

It is remarkable to highlight, defects in skin barrier structure, as well as impairment in functional integrity and reduced ability for self-renewal, seem to play a role in triggering both an immune response and nonspecific inflammatory reaction [2].

Atopic children show equally important immune deregulation, probably due to a change in the cytokine profile synthesized by Th1 and Th2 subpopulations. A shortage in Th1 subpopulation observed in these patients is associated with reduced secretion of interferon (IFN) gamma which in turn may reduce the activity of natural killer (NK) cells, decrease the number of circulating T lymphocytes and result in an elevated ratio of CD4+/CD8+ lymphocytes [2]. These cells secrete interleukins (IL-4, IL-5 and IL-13) which induce the production of immunoglobulin E (antibody

present in allergies). Also, an exacerbation of itching is the main symptom of atopic dermatitis [3]. As atopic dermatitis involves diverse genetic abnormalities which affect both the barrier function and the immune system, mutations have been detected in two major groups of genes: genes encoding structural epithelium proteins and genes encoding elements of the immune system. The family of genes of the epithelial differentiation complex is located in chromosome 1, and there is specially one important; filaggrin (FLG), an epidermal protein, with a very important role in the synthesis of keratinocytes [4]. Thus, there is an area of the genome in chromosome 5 that participates in the synthesis of cytokines related to the regulation of chemical signals, interleukins 4, 5, 12 and 13 and the granulocyte-macrophage colony-stimulating factor (GM-CSF) [5]. The atopic phenotype results from the interaction of multiple genes.

Epidermal barrier proteins, including FLG, transglutaminase, keratin, loricrin and intercellular proteins, are cross-linked to form an impermeable skin barrier. A defective regulation of genes encoding proteins that degrade intercellular junctions (proteases) makes the epidermis more permeable with loss of adhesion between desmosomes or alteration in the production of ceramides (lipids that prevent transepidermal water loss) [6]. A disrupted skin barrier allows entry of allergens and leads to systemic allergic responses such as increased IgE. The stratum corneum contributes greatly to skin barrier function. Transepidermal water loss (TEWL) is a non-invasive *in vivo* measurement of water loss through the *stratum corneum* to evaluate skin barrier function. Skin in patients with atopic dermatitis always presents microscopic injuries even in the remission. These micro-cracks allow the entry of pathogens, allergens and irritants that contribute to inflammation, infection and increase in TEWL. Likewise, there are other factors that influence the pathogenesis of AD, including: microbial colonization, scratching and exposure to allergens (carrying proteases).

Clinically, AD is characterized by intense itching, dry skin and periodic outbreaks of eczematous lesions of different severity usually observed in a characteristic age-dependent distribution with facial, scalp and extensor involvement in infants and young children, and predominant flexural involvement in older children and adults. The disease usually appears in the first years of life and the location of eczema varies with age [7]. The impact of this disease produces a decline of quality of life and negatively modifies the social, academic and occupational spheres. Sleep disturbance is a frequently consequence which increases various problems such as: low school performance, difficulties in sporting activities, social rejection and anxiety, and may be the cause of psychological problems in pediatric patients with AD [8]. Often it causes irritability and triggers the need for scratching, which further worsens the fragility of the skin barrier. The itching is not mediated by histamine, but other inflammatory mediators are involved [9]. Therefore, oral antihistamines often don't work successfully in relieving itching so the motivation for using them is their sedative effect. In several studies based on quality of life which were carried out in school populations in different countries, over 90% of children have emotional alterations that correlate with the severity of the disease.[9-10] Due to its chronic development, the high impact on the quality of life of patients and their families, and its high prevalence in many countries, doctors and patients require adequate strategies to keep patient free of symptoms during remission and improve their quality of life.[10]

The prevalence of AD is estimated to be 15-20% in children and 1-3% in adults, and the incidence has increased by 2- 3 times over the past decades in industrialized countries [11]. Literature reports that the incidence is similar in both genders, but there are ethnic and geographic differences that suggest the influence of environmental factors in the outcome of the disease. Furthermore, there is a genetic predisposition to suffer from the disease as previously mentioned. The prevalence of AD in children with affected first and second-degree relatives can reach 39% and 19% respectively [11]. AD usually appears between 3 and 6 months of age so that 60% of the cases appear in the first year [12] and around 85% are diagnosed before the age of five. The prevalence of AD in the general population is difficult to determine, but it is estimated that in advanced industrialized countries, around 20% of children suffer from the disease [11, 13]. Most children who suffer from atopic dermatitis don't

present symptoms in adulthood, but it is estimated that between 10 and 30% of patients will continue to suffer from it during adult life [14].

Pharmacological treatment must be individually determined for each patient, identifying and correcting triggering factors, determining the extent and location of the lesions, as following its evolution. Frequent application of unscented moisturizers as necessary reduces dryness and itching and helps prevent flares. Epidermal barrier function is preserved and long periods free of symptoms are achieved with the application of appropriate moisturization twice daily. These results involved less steroid treatment, which is a challenge for dermatologists. Consequently, a new cosmetic treatment has been developed to palliate symptoms and extend the remission period between relapses by Cantabria Labs. Dermacare Lotion is formulated with a highly emollient system that enhances skin hydration, as well as the strengthening and repair of the skin barrier function. This emollient formula is supplemented with Pro-Filaggrin Complex, polidocanol, urea, xylitol and glycyrrhetic acid. Pro-Filaggrin Complex, which is composed by a glucomannan derived from the yeast *Candida utilis*, galactoarabinosa and Niacinamide, reduces typical AD pruritus and its associated scratching. Pro-Filaggrin Complex strengthens skin barrier by inducing the expression of filaggrin gene. 3% polidocanol and 5% urea act as antipruritic agents. Xylitol and glycyrrhetic acid provide antibacterial and specific protection against biofilm alteration to prevent cutaneous microbiome imbalance, avoid superinfection by *Staphylococcus aureus*, and decrease inflammation, which would lead to exacerbation of erythema and pruritus. Dermacare Syndet Cleanser is formulated to mitigate pruritus, induce the production of filaggrin and reduce skin inflammation.

Used daily, Dermacare Lotion and Syndet (Cantabria Labs) maintain skin hydration, support barrier function and reduce TEWL and desquamation index.

2. Study Description

This study was a prospective, pilot, open-label and multicenter trial. Eight-week clinical studies were conducted to assess the efficacy and safety of this new cosmetic product for the treatment of children diagnosed with mild to moderate atopic dermatitis during remission. The study was carried out by two different pediatric dermatology departments at the La Paz University Hospital (Madrid) and University Clinic of Navarra (Spain). The participating subjects had to have completed a 2-week corticosteroid-wash-out period of 2 weeks, as well as avoid the use of moisturizing creams starting 48 hours before the beginning of the trial.

The primary outcome was to determine the safety of the new cosmetic product, so any adverse events were recorded, and the investigator assessed the severity of skin irritation caused by the product based on erythema, flaking, pruritus and lichenification. The secondary outcome was to determine the efficacy of the product after the treatment period and to assess the persistent effect of Dermacare after period with habitual treatment. Efficacy was evaluated by means of objective and subjective parameters. The new cosmetic formulation was applied to patients twice daily for 28 days. One of the times, the lotion had to be applied after bathing with Dermacare Syndet cleanser. During this period, oral and topical steroids were not allowed. The nineteen patients were assessed during 3 visits (day 0, day 14 and day 28). After the first 28 days, Dermacare treatment was suspended and patients returned to their normal hygiene and moisturizing routines until day 56 when they were assessed a fourth time (Visit day 56).

3. Patients and Method

The patients with AD who met eligibility criteria, and gave written informed consent were enrolled in this study. The inclusion criteria were children aged 6 months to 3 years with mild-to-moderate AD (according to Scoring Atopic Dermatitis [SCORAD]), with no acute lesions or in remission period, and with Informed consent from parents/guardians of children. A total of nineteen subjects were recruited. Patients didn't use pharmacological treatment during 2 weeks prior to the

study or emollient during 48 h previous of the study or presenting any allergy to the any of the ingredients in the lotion under study were excluded. Adverse events were recorded throughout the study. Likewise, the dermatologist investigators and the subjects completed efficacy and tolerability assessments at baseline, 14 days, 28 days and 56 days (V1, V2, V3 and V4, respectively). Clinical assessment through objective parameters, record of adverse events and subjective parameters (Patient/Investigator Global Assessment and Parent's Index of Quality of Life Index and Questionnaire for product evaluation by parents, and tolerance by investigator) were developed by dermatologists.

Transepidermal Water Loss (TEWL) was measured using a Tewameter® TM 300 device (Courage + Khazaka electronic GmbH). TEWL is an indispensable parameter for the evaluation of the skin's water barrier function and even the slightest modification can be identified at an early stage. The device measures the density gradient of water evaporation (g/h/m²). Measurements were carried out on the right forearm and right cheek. Desquamation index was measured using Tape-Stripping technique with a Cornefix® F 20 device. It consists in a special adhesive foil which collects corneocytes. The number, size and thickness of the corneocytes indicate the desquamation/hydration level of the Stratum corneum. When mounted on the Visioscan® camera, the desquamation can be evaluated by its software. The adhesive side of the Corneofix® is applied to the skin area to be evaluated for only a very short time. On removing the tape from the skin, the corneocytes adhere to it. When skin is dehydrated, or damaged, it is characterized by thickened scales and flakes of different sizes. When properly moisturized, however, skin presents regular and small regular corneocytes. Clinical severity was evaluated on a scale of skin irritation, where the investigator established the severity of the pathology based on erythema, scaling, pruritus and lichenification (0-absent, 1-mild, 2-moderate, 3-severe), and by EASI (Eczema Area and Severity Index) which consists in the measurement of the severity and extent of atopic eczema. EASI score does not include a grade for dryness or scaling and it includes only inflamed areas. Area score is recorded for four regions of the body (head and neck, trunk, upper limbs and lower limbs). The area score is the percentage of skin affected by eczema for each body region. Severity score is recorded for each of the four regions of the body. The severity score is the sum of the intensity scores for four signs (redness, thickness, scratching and lichenification). The average intensity of each sign in each body region is assessed as: none (0), mild (1), moderate (2) and severe (3).

The Parents' Index of Quality of Life in Atopic Dermatitis (PIQoL-AD) is a Dermatological questionnaire regarding the quality of the child's life as assessed by the patient's parents or guardians. It was developed for use in parents of pediatric AD patients, and it is a very useful tool in many studies. The PIQoL-AD score discriminates between different levels of severity and usually correlates with the subjective clinical intensity of atopic dermatitis. The final value of the questionnaire ranges from 0 (highest score) to 28 (lowest score) [15.] Other subjective parameters such as Parent Global Assessment (PGA), Investigator Global Assessment (IGA), a questionnaire for product evaluation by parents and one for assessing product tolerability by the investigator (0: not tolerated - 3: high tolerance), were performed.

3.1. Statistical analysis

For the analysis of the evolution of quantitative parameters over time, and due to the great variability, that were presented some data collected in the study, not following a Gaussian distribution, the non-parametric Friedman's test as a global test. For pair comparisons (interindividual) between baseline and following visits, the non-parametric Wilcoxon test was used. Statistical analysis was performed by SPSS software V24.0, with differences being considered as significant when the significance values obtained from the hypothesis contrast were less than 5% ($p < 0.05$).

4. Results

17 of the 19 enrolled patients finished the treatment protocol. The 2 patients were drop-out for reasons not related to the cosmetic treatment. All 19 volunteers were however included in the analysis (an intention-to-treat, ITT). The total number of patients included in the study presented an average age of 18 months, having had the disease for an average of 13.4 months and with an average of 3.5 relapses over the preceding 6-month period. No side effects were reported, apart from typical effects under remission-recurrence cycle of atopic dermatitis.

After 14 days treatment with the new formulation, there was a significant 36.7% decrease ($p = 0.035$) in TEWL on the forearm vs baseline (falling from 25.4 to 16.08 g/m²h), and a 25.7% reduction in TEWL (statistical trend $p = 0.061$) on the cheek. After 28 days treatment, TEWL reduction was 29.1% on the forearm and 20.25% in the cheek, not reaching statistical significance ($p = 0.363$ and $p = 0.334$) due to very high intra-individual variability and small sample size (Figure, 1).

The analysis according to desquamation index was carried out only on those patients (Figure 2). A reduction in desquamation was observed in 69% of patients at 14 days and in 70% of patients at 28 days. The mean reduction in desquamation index at 14 days was 30.95% and 21% at 28 days. The global average decrease in desquamation index in the total population analyzed at both 14 and 28 days, although it did not reach statistical significance ($p = 0.215$ and $p = 0.208$, respectively), shows a decrease, as it was previously reported.

The data obtained from the EASI (Eczema Area and Severity Index) used for initial assessment and monitoring during treatment showed a clear and significant improvement over time. The decrease in the severity index score was 45% after 14 days treatment, representing a significant trend ($p = 0.066$). A significant improvement was achieved after 28 days of treatment ($p = 0.002$), with a decrease of 70.4% in the EASI score vs baseline. The EASI showed a progressive and significant decrease in severity of signs of atopic dermatitis, being a parameter of efficacy. Dermacare brought about a significant reduction in the severity of basal atopic dermatitis, in only 28 days, with improvement beginning to appear at 14 days. Investigator global assessment (IGA) reported a significant improvement of 27% ($p = 0.013$) after 28 days of treatment. After the patients returned to their normal treatment, a global worsening of 38.5% was observed by the investigators. Likewise, parent global assessment (PGA) indicated a significant improvement of 38.5% ($p = 0.05$) after 28 days of treatment with Dermacare. When the patients returned to the normal treatment, PGA scores got worsen by 42.31% in comparison to the PGA score after 28 days of treatment with Dermacare (Figure 3).

Treatment tolerance was reported as very good from beginning to end of the study. The quality of life questionnaire (PI-QoL) was administered at baseline visit, after 28 days of treatment with Dermacare and the last visit 28 days after returning to normal treatment. PI-QoL score significantly improved after 28 days of treatment with Dermacare, passing from 7.7 + 4.6 to 4.9 + 3.3, representing a significant improvement of 36.4% ($p = 0.046$) (Fig.2). After completing the period of normal cosmetic treatment, patient quality of life worsened with respect to the score obtained after therapy with Dermacare. The mean score increased to 5.6 + 3.7, still representing however a significant improvement of 27% vs baseline ($p = 0.05$). The parent product evaluation questionnaire gave a 90% positive product rating. A significant decrease in skin irritation was observed after 28 days of treatment with Dermacare ($p = 0.024$). The skin irritation value decreased by 55.6% between days 14 and 28.

5. Discussion

In literature many authors emphasize the importance of hydration in atopic skin. Body Cream reduces the incidence of flare and the time to flare, reinforcing guidelines that recommend daily emollient therapy as an integral part of maintenance treatment to prevent flares [16, 17, 18]

After 14 days treatment with Dermacare, a significant increase in cutaneous moisturization was observed due to a decrease in transepidermal water loss vs baseline. After 28 days of treatment, there was still improvement in moisturization resulting from a 30% decrease in TEWL, although it was not significant with respect to baseline. It should be said at this point that statistical significance was difficult to obtain for TEWL values as at 28 days only 15 patients were analyzed for this parameter vs 19 at baseline. TEWL values observed during the baseline visit in the study population were similar to those referenced in literature regarding patients with atopic dermatitis [19]. The continued use of Dermacare for 14 and 28 days decreased transepidermal water loss, approaching values considered to be normal in children without AD.

A decrease in desquamation was observed although statistical significance was not reached. This fact is undoubtedly due to two main factors: that inclusion criteria required patients presenting no active AD lesions and thus the stripping sample was taken from a standardized "healthy skin" area of the patient, the small sample size. These findings are supported by the reduction in desquamation observed after the treatment with Dermacare. After 14 and 28 days of treatment a 20% and 30% reduction in desquamation was observed in most patients. However, no statistical significance was determined possibly due to the sample size. The EASI severity index showed a significant decrease after just 14 days of treatment, reaching a 70% decrease compared with the baseline. We emphasize that only with 28 days of treatment there is a significant reduction in the severity of atopic dermatitis symptoms. TEWL, desquamation index and EASI are objective parameters which suggest that treatment with Dermacare restores skin hydration and decreases the severity of signs present in patients with atopic dermatitis.

The subjective parameters analyzed in the study show that both investigators (IGA) and parents (PGA) reported significative improvement, with an increase in the value given by the investigators of 27%, and 38,4% in the evaluation of the parents/legal guardians of the patient, and both improvements were statistically significant. After returning to the normal treatment for 28 days (visit 4), IGA reported a remarkable reduction of 38.5 % compared to the one evaluated after 28 days with the Dermacare treatment (visit 3). PGA reduction was 42.3%. After finishing the period with usual cosmetic treatment, the quality of life of the patient got worse with respect to the score obtained after therapy with Dermacare. The mean score increased to 5.6 + 3.7. However, regarding the score of the baseline visit was obtained a significant improvement of 27% ($p = 0.05$). The worsening observed after discontinuing Dermacare treatment, at times returned to values to achieved at 14 days with Dermacare, allows us to confirm that to preserve the improvement obtained with this new formula, this treatment must be continued for a longer period of time. In addition, there was a positive correlation between the opinion of the investigators and the parent regarding the improvement achieved with the treatment and in the Dermacare worsening after stopping the treatment. Quality of life showed a significant improvement after 28 days of treatment with Dermacare. After discontinuing the treatment and returning to normal treatment, a slight, but significant worsening of the quality of life was observed. These significant differences demonstrated the importance of maintenance treatment with specific moisturizers in order to improve quality of life of patients with atopic dermatitis. We must highlight that Dermacare showed very good tolerance and no adverse effects were reported during treatment

6. Conclusions

Despite the high variability of the objective data and the small study sample size due to the pilot nature of the study and drop the population at visit 2 (28 days with treatment); cutaneous moisturization of patients with AD improves with Dermacare treatment. This affirmation is supported by the decrease in the values of transepidermal water loss (TEWL) and the reduction in skin flaking. Some authors report that treatment with an adequate moisturizer is beneficial for the dry skin of patients with AD specially during the dry, cold season [16]. Treatment with Dermacare

restores the skin barrier by increasing the cutaneous hydration observed as a result of the reduction of cutaneous desquamation and transepidermal water loss. We obtained cutaneous hydration values similar to those described by Choi SJ *et al.* [19] in children without atopic dermatitis. The restoration of the skin barrier promotes optimal hydration and prevents the penetration of external agents such as allergens or microorganisms that cause worsening of atopy symptoms. The positive results obtained in the objective parameters were supported by the improvement reported by both the investigators and the parents of the patients, and by the improvement in quality of life.

The fact observed that improvement during the treatment with Dermacare and the worsening when it was discontinued, suggested that maintenance treatment during remission can increase time between relapses. Likewise, Dermacare could give support to decrease the number of times, in which is necessary the use of corticosteroids and consequently, the possible occurrence of side effects as a result of their use. However, it is believed that further studies are warranted to confirm the hypothesis of prolonging the corticoid-free period to avoid skin dystrophy typical of corticoid use.

Funding: This study was partially supported by Cantabria Labs, SA

Institutional Review Board (IRB): This study has been reviewed and approved by the IRB

Conflict of Interest Disclosure: Azahara Perez Davó is Scientific Advisor of Cantabria Labs. Dra Cristina García Millán serves as a part-time consultant for Cantabria Labs. The remaining authors have no conflicts of interest to declare

Figures

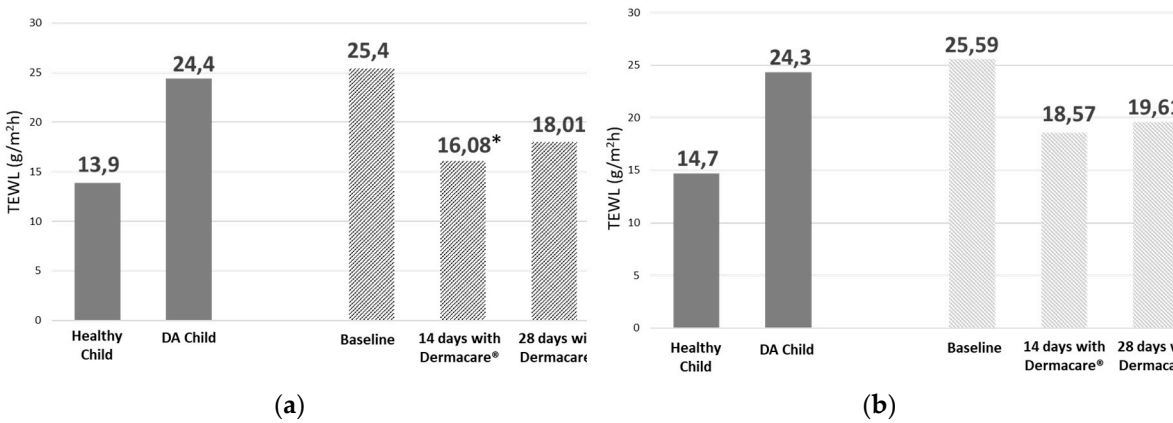


Figure 1. TEWL values (g/m²h) in healthy children and children with AD (mean±SD) [19]; mean TEWL values at baseline and after 14 and 28 days with Dermacare®. Evaluations in forearm (a) and cheek (b). *p=0,035

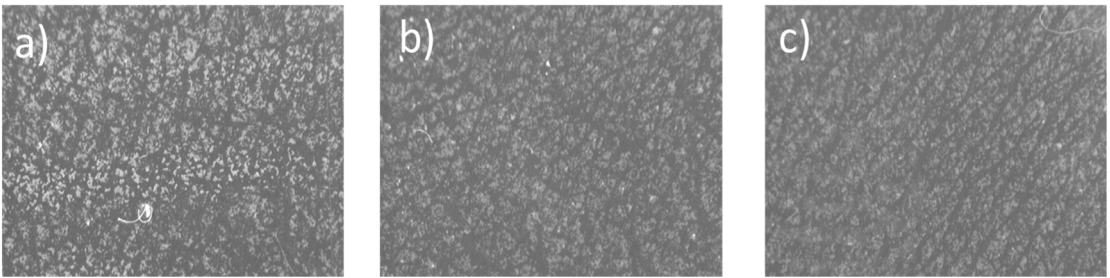


Figure 2. Desquamation index was measured used Cornefix® F 20 device. Images taken by Visioscan® camera. (a) Baseline; (b) 14 days with Dermacare; (c) 28 days with Dermacare.

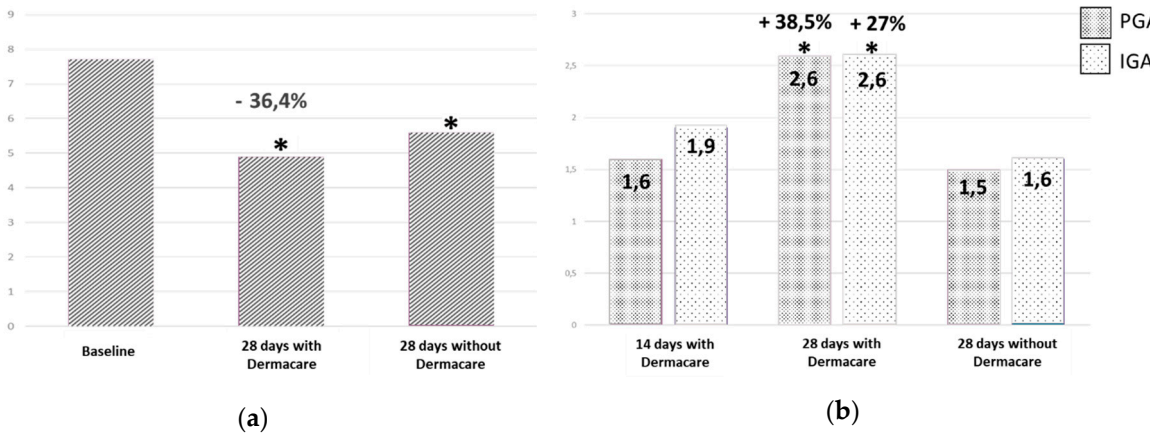


Figure 3. Subjective evaluations: Parents' Index of quality of Life [15] (a), whose interval is between 0 (highest score) and 28 (lowest score) and Patient/Investigator Global Assessments (IGA/PGA) (b). *p < 0,05

References

1. Kim BE, Leung DYM. Significance of Skin Barrier Dysfunction in Atopic Dermatitis. Allergy Asthma Immunol Res. 2018 May;10(3):207-215
2. Nowicka D1, Grywalska E2. Role of Immune Defects and Colonization of Staphylococcus aureus in the Pathogenesis of Atopic Dermatitis. Anal Cell Pathol (Amst). 2018 May 2;201
3. Nishio Y, Noguchi E, Shibasaki M, et al. Association between polymorphisms in the SPINK5 gene and atopic dermatitis in the Japanese. Genes Immun. 2003; 4: 515-517
4. Cookson W. The immunogenetics of asthma and eczema: a new focus on the epithelium. Nat Rev Immunol. 2004; 4: 978-988.
5. Vasilopoulos Y, Cork MJ, Murphy R, et al. Genetic association between an AACC insertion in the 3'UTR of the stratum corneum chymotryptic enzyme gene and atopic dermatitis. J. Invest Dermatol. 2004; 123: 62-66.
6. Carbone A, Siu A, Rupal Patel. Pediatric atopic dermatitis: a review of the medical management. Ann Pharmacother. 2010; 44 (9): 1448-58
7. Suárez-Fariñas M, Tintle SJ, Shemer A, Chiricozzi A, Nogales K, Cardinale I, et al. Non lesional atopic dermatitis skin is characterized by broad terminal differentiation defects and variable immune abnormalities. J Allergy Clin Immunol. 2011; 127 (4): 954-64
8. Schlapbach C, Simon D. Update on skin allergy. Allergy. 2014; 69 (12): 1571-81 Simon D. Systemic therapy of atopic dermatitis in children and adults. Curr Probl Dermatol. 2011; 41: 156-64.
9. Sampogna F, Finlay AY, Salek SS, Chernyshov P, Dalgard FJ. Measuring the impact of dermatological conditions on family and caregivers: a review of dermatology-specific instruments. J Eur Acad Dermatol Venereol. 2017
10. Cheok S, Yee F, Ma JYS, Leow R, Ho MSL, Yew YW, Tay YK, Rebello SA, Luo N, Koh MJA. Prevalence and Descriptive Epidemiology of Atopic Dermatitis and Its Impact on Quality of Life in Singapore. Br J Dermatol. 2017 Apr 17
11. Nutten S et al. Atopic dermatitis: global epidemiology and risk factors. Ann Nutr Metab. 2015;66 Suppl 1:8-16.
12. Ellis CN, Mancini AJ, Paller AS, Simpson EL, Eichenfield LF. Understanding and managing atopic dermatitis in adult patients. Semin Cutan Med Surg 2012; 31: S18-22.

366 13. Blanco QA, Díaz Castella JM, Balañá Vilanova M, Valveny Llobet N. Risk factors for atopic dermatitis and
367 familial prevalence in Spain (ELIHO study)]. *An Pediatr (Barc)*.2005; 63: 480-488.

368 14. Avena-Woods C. Overview of atopic dermatitis. *Am J Manag Care*. 2017; 23 (8 Suppl): S115-S123.

369 15. De Lucas R, González-Enseñat MA, Giménez A, Puig L, Vicente A, Díaz JM, Whalley D, McKenna S, Baró
370 E. Validation of Spanish versions of Parents' Index of Quality of Life in Atopic Dermatitis (PIQoL-AD) and
371 Quality of life Index for Atopic Dermatitis (QoLIAD) questionnaires: an international study. *Actas*
372 *Dermosifiliogr*. 2003; 94 (8): 539.

373 16. Kikuchi K, Tagami H. Japanese Cosmetic Scientist Task Force for Skin Care of Atopic D. Noninvasive
374 biophysical assessments of the efficacy of a moisturizing cosmetic cream base for patients with atopic
375 dermatitis during different seasons. *Br J Dermatol* 2008; 158: 969-78.

376 17. Weber TM, Samarin F, Babcock MJ, Filbry A, Rippke F. Steroid-Free Over-the-Counter Eczema Skin Care
377 Formulations Reduce Risk of Flare, Prolong Time to Flare, and Reduce Eczema Symptoms in Pediatric
378 Subjects with Atopic Dermatitis. *J Drugs Dermatol*. 2015; 14 (5): 478-85

379 18. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL et al. Guidelines of care for
380 the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad*
381 *Dermatol*. 2014; 70 (2): 338-51.

382 19. Choi SJ, Song MG, Sung WT, Lee DY, Lee JH, Lee ES, et al. Comparison of transepidermal water loss,
383 capacitance and pH values in the skin between intrinsic and extrinsic atopic dermatitis patients. *J Korean*
384 *Med Sci*. 2003; 18 (1): 93-6.