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Clinical and hardware evaluation of moisturizing properties and tolerability of a emollient cream with filagrinol ("Admera") in atopic dermatitis in children

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S. S. Masalskiy [1,2], **Yu. S. Smolkin** [1,2,3], **O. Yu. Smolkina** [1]

[1] *Scientific-Clinical Consultative Center of Allergology and Immunology, 6 Ostrovityanova st., 117513, Moscow, Russia*

[2] *Association of Pediatric Allergists and Immunologists, 6 Ostrovityanova st., 117513, Moscow, Russia*

[3] *Academy of Postgraduate Education of the Federal State Budgetary Institution Federal Scientific and Practical Center of the Federal Medical and Biological Agency of Russia, 91 Volokolamskoe Shosse, 125371, Moscow, Russia*

Masalskiy Sergey Sergeevich — Candidate of Medical Sciences, Deputy secretary Association of Pediatric Allergists and Immunologists, ORCID ID 0000-0002-2048-5709, e-mail: masalsky@live.com.

Smolkin Yuri Solomonovich — Doctor of Medical Science, Professor of Department of Clinical Immunology and Allergology of the Academy of Postgraduate Education of the Federal State Budgetary Institution Federal Scientific and Practical Center of the Federal Medical and Biological Agency of Russia, vice-president of Association Pediatric Allergist and Immunologist Russia (APAIR), allergist-immunologist of Scientific-Clinical Consultative Center of Allergology and Immunology. ORCID ID 0000-0001-7876-6258, e-mail: smolking@df.ru.

Smolkina Olga Yurievna — dermatologist of Scientific-Clinical Consultative Center of Allergology and Immunology, ORCID ID 0000- 002-3235-6461, e-mail: o.smolkina@adair.ru.

Abstract

Objective. Evaluate the possibility of using a cream with 5% filagrinol («Admera») in children (0–18 years old) as an emollient in atopic dermatitis (AtD) and receive hardware measurements of skin hydration.

Materials and methods. Open interventional study in parallel groups of children with AtD 0–18 years old (n = 72, median age 6 [3.75; 7.0] years). 2 equal groups: group 1 received methylprednisolone cream 1 time daily on lesions for 14 days + Admera emollient on the other skin; group 2 received the same treatment + cream with filagrinol 5% applied from day 5 on the lesions.

Results. Standard therapy with topical steroids was effective. The severity indices during steroid + emollient treatment decreased significantly: EASI 11.5 [6.0; 17.0] vs 2 [1; 3.8] scores, $p < 0.001$; skin lesion area from 17.5% [10.0; 26.8%] to 3.5% [1.25; 6.0%], $p < 0.001$; IGA score — 2 [2; 3] vs 1 [1; 2], $p < 0.01$.

The total itching score for AtD (max 10) became significantly lower with therapy: nocturnal itching decreased from 3 [1; 7] to 1 [1; 3] and daytime itching from 4 [3; 7] to 2.5 [1; 4] points, $p < 0.01$.

The mean values of hardware-measured skin hydration outside the lesion areas were 8 [6.0; 12.0] units at baseline. After 14 days of emollient, hydration of dry clear skin increased to 10 [8.0; 15.0] units ($p = 0{,}017$). The hydration of the skin on the affected areas increased significantly from 8 [6; 10] to 12.0 [8; 15] units ($p = 0.001$).

The patients' organoleptic evaluation of the cream was 4.48 (max 5). No serious or moderate adverse events (AEs) were reported in this study. In 11.3% of cases, the skin itching was detected, but resolved rapidly without treatment.

Conclusion. The cream with 5% filagrinol («Admera») significantly improved skin hydration, as measured instrumentally, in the area of dermatitis and dry skin without ones. The cream caused no significant adverse reactions and could be used together with topical steroids.

Keywords: dermatitis, filaggrin, filagrinol, children, hydration.

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For correspondence:
Sergey S. Masalskiy, candidate of science, Executive Secretary of Association Pediatric Allergist and Immunologist Russia (APAIR), allergist-immunologist of Scientific-Clinical Consultative Center of Allergology and Immunology.

Address: 6 Ostrovityanova st., 117513, Moscow, Russia.

E-mail: masalskysergey@yandex.ru.

Для корреспонденции:
Масальский Сергей Сергеевич, кандидат медицинских наук, врач аллерголог-иммунолог ООО «НККЦ аллергологии и иммунологии», ответственный секретарь Ассоциации детских аллергологов и иммунологов России.

Адрес: 117513, Российская Федерация, Москва, ул. Островитянова, д. 6.

E-mail: masalskysergey@yandex.ru.

Клиническая и аппаратная оценка свойств и переносимости крема с филагринолом («Адмера») при атопическом дерматите у детей

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С. С. Масальский [1,2], Ю. С. Смолкин [1,2,3], О. Ю. Смолкина [1]

[1] *ООО «НККЦ аллергологии и иммунологии», Москва, 117513, ул. Островитянова, д. 6, Россия*

[2] *Ассоциация детских аллергологов и иммунологов России, Москва, Россия*

[3] *Академия постдипломного образования ФГБУ ФНКЦ ФМБА России, Москва, Россия*

Масальский Сергей Сергеевич — к. м. н., ответственный секретарь Ассоциации детских аллергологов и иммунологов России, врач аллерголог-иммунолог; ORCID ID 0000-0002-2048-5709, e-mail: masalsky@live.com.

Смолкин Юрий Соломонович — д. м. н., профессор кафедры клинической иммунологии и аллергологии Академии постдипломного образования ФГБУ ФНКЦ ФМБА России, вице-президент Ассоциации детских аллергологов и иммунологов России, врач аллерголог-иммунолог ООО «НККЦ аллергологии и иммунологии», ORCID ID 0000-0001-7876-6258, e-mail: smolking@df.ru.

Смолкина Ольга Юрьевна — врач-дерматолог ООО «НККЦ аллергологии и иммунологии», ORCID ID 0000-002-3235-6461, e-mail: o.smolkina@adair.ru.

Абстракт

Цель — оценить возможность применения крема с 5 %-м филагринолом («Адмера») у детей (0–18 лет) в качестве эмолента при атопическом дерматите (АтД) и получить инструментальные данные об увлажненности кожи.

Материалы и методы. Открытое интервенционное исследование в параллельных группах детей с АтД 0–18 лет (n = 72, медиана возраста 6 [3,75; 7,0] лет). 2 равные группы: 1-я получала крем метилпреднизолона 1 р/сут на очаги поражения в течение 14 дней + эмолент «Адмера» на остальную кожу; 2-я группа — аналогичное лечение + крем с 5 %-м филагринолом наносился начиная с 5 дня на очаги поражения.

Результаты. Стандартная терапия применением топического глюкокортикостероида в комплексе с эмолентом была эффективна. Индексы тяжести на фоне лечения стероид + эмолент достоверно снижались: EASI 11,5 [6,0; 17,0] vs 2 [1; 3,8] балла, $p < 0,001$; площадь поражения кожи с 17,5 % [10,0; 26,8 %] до 3,5 % [1,25; 6,0 %], $p < 0,001$; оценка IGA 2 [2; 3] vs 1 [1; 2], $p < 0,01$.

Оценка общего зуда при АтД (max 10) на фоне терапии стала достоверно меньше: ночной зуд снизился с 3 [1; 7] до 1 [1; 3] и дневной зуд с 4 [3; 7] до 2,5 [1; 4] баллов, $p < 0,01$.

Средние применения аппаратно измеренной увлажненности кожи вне очагов поражения исходно составили 8 [6,0; 12,0] ЕД. После 14 дней эмолента увлажненность сухой чистой кожи увеличилась до 10 [8,0; 15,0] ЕД ($p = 0,017$). Увлажненность кожи на пораженных участках достоверно повысилась с 8 [6; 10] до 12,0 [8; 15] ЕД ($p = 0,001$).

Органолептическая оценка крема пациентами составила 4,48 балла (max 5). В ходе настоящего исследования не было зарегистрировано случаев развития нежелательных явлений (НЯ), отвечающих критериям серьезной или умеренной силы реакции. 11,3 % пациентов отмечали проявления кожного зуда, который быстро купировался без лечения.

Заключение. Крем с 5 %-м филагринолом («Адмера») достоверно повышает увлажненность кожи, измеренную инструментально в области высыпаний и сухой кожи без очагов дерматита. Крем не вызывает значимых побочных реакций и может использоваться совместно с топическими стероидами.

Ключевые слова: дерматит, филаггрин, филагринол, дети, увлажненность.

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INTRODUCTION

Atopic dermatitis (AtD) is a genetically determined disease and depends on the degree of the impaired epidermal barrier disruption and dysfunction of immune response [1]. Inflammation endotypes, involving other important cytokines (TSLP, IL33, Th17, etc.) [2] are described despite usual prevalence of immunological disorders by Th2-type in this disease. Similar is the case with barrier disorders: filaggrin [3] remains the most studied although numerous disturbances of lipid synthesis, ceramide and loricrin have been described.

The baby's skin is significantly different in its properties than the skin of an adult. It is more permeable and can be exposed to adverse environmental factors. Atopic dermatitis occurs in early childhood much more frequently than in adults. Genetic defects in filaggrin protein synthesis, ensuring the normal functioning of the epidermal barrier, appear in 10 % of Europeans [4]. Filaggrin is involved in forming the outer layer of skin and disturbance in its structure is associated with the severity of atopic dermatitis and its from. In the cohort to COPSAC (Denmark) 43 % of children, born to mothers with bronchial asthma, experienced developing atopic dermatitis and 15 % of them were detected zero mutation in R501X and (or) 2282del4 loci, responsible for FLG synthesis [5]. This data does not include zero mutation (described more than 40) and impaired protein function. Apparently, the role of filaggrin is much broader as there is evidence of associating the deficiency of this protein with bronchial asthma and atopic march. In accounting for several mutations, up to 50 % of patients have various filaggrin dysfunctions [6]. Evaluating the number of mutations and filaggrin abnormalities in the skin causes more difficulties as they may have a local character. For instance, O.Yu.Smolkina's study (2021) shows that the amount of DNA damage and gene methylation in the affected areas and on healthy skin in patients with AtD was different [7].

Filaggrin is a major structural component, responsible for moisture saturation and retention in the skin, it provides structuring cytoskeleton of horny cells and stimulating the production of epidermal lipids. With filaggrin deficiency in the epidermis, there is density loss by coreodesmosomes and defective structure of cornified "envelopes", its degradation products are involved in forming the natural moisturizing factor. The end products of protein metabolism contribute to the maintenance of pH on the skin surface within the physiological norm [8].

In the complex of therapeutic measures use of moisturizers is considered to be basic and obligatory at all stages of treatment in the defectiveness of the skin barrier [9]. Emollients themselves can reduce inflammation and the severity of a patient's condition with AtD. Moreover, their use decreases the frequency and amount of anti-inflammatory drugs, required in treating AtD. Emollients can be the main cosmetic basic tool to treat children with diseases of mild severity and part of moderate and severe AtD treatment [10].

Topical steroids are first-line drugs for atopic dermatitis therapy in all groups of patients, including children aged 4 months, pregnant women and nursing mothers. Efficiency of modern non-fluorinated corticosteroids allows to arrest inflammation and move quickly to use proactive therapy if needed. In milder forms of AtD high anti-inflammatory activity suppresses local inflammation in the skin and further allows to maintain remission exclusively by emollients. Applying emollients together with corticosteroids in lesions is already possible in the subacute period of the disease [11].

The composition of "ideal" emollient should contain substances with different skin's moisture retention mechanisms, such as humectants (direct humidifiers, retaining water molecules), occlusive substances, keratolytic components, eliminating microcracks [12]. Occlusive compounds, such as petrolatum and mineral oil, form a film on the skin's surface and prevent water evaporation. Humidifiers (glycerin, lactic acid, urea) attract and retain water. The presence of physiological lipids (cholesterol, ceramides and free fatty acid) in cosmetics allows to fill up intercellular spaces between keratinocytes and partially restore their barrier and moisture-retaining functions [13]. Emollients of the new generation contain not only moisturizing components, but also reducing epidermal barrier substances. Natural oils and ceramides, included in the lamellar plate of the lipid layer in the intercellular space [14] have become commonplace in moisturizers. It is recommended to use cosmetic products, devoid of protein allergens and haptens (capable to cause contact allergy), especially in children under 2 years old.

Rational skin care along with avoiding allergic and physical triggers is the key to successful maintenance of AtD remission. Adequate skin cleansing and moisturizing lead to normalizing the epidermal barrier, reducing skin dryness and transepidermal moisture loss. It is assumed that the use of emollients of the new generation, affecting the structure and functional activity of

the epidermal barrier, is an essential component in accelerating the onset of dermatitis remission, preventing its relapses and increasing skin hydration [15].

The information on skin hydration could be useful in routine practice. However, hardware measurements of hydration is usually difficult due to the instrument unavailability and a doctor has to rely exclusively on the clinical signs. Additional components are positioned to offer patients benefits when using the cosmetic product, however, this issue requires further research.

Emollients of the new generation, denoted as "emollients-plus", include the active compounds that affect the microbiome and the functional activity of the epidermal barrier, providing in the long run additional benefits to patients with atopic dermatitis. In particular, filaggrin, activating the synthesis of its own filaggrin, helps to restore homeostasis in the stratum corneum, to maintain its protective functions as well as high hydration level and physiological pH level [16].

Appearance of "emollient-plus" "Admera" with 5 % filagrinol in practice should improve patient's skin hydration. Russian studies obtained data of this filagrinol containing cream influence on the level of skin hydration when using it for 4 and 12 weeks [17, 18].

Of particular interest is the study of possibilities for combining the cream with filagrinol and topical steroids during the relief of dermatitis exacerbations and ascertaining benefits and secure concomitant product use. At the planning stage of the clinic trial it was assumed that the use of the cosmetic product "Admera" by children of different age groups with atopic dermatitis during the course of standard therapy will increase the patient's adherence to treatment, contribute to more effective relief of the disease symptoms, in particular, promoting skin hydration and softening, reduce subjective sensations, stimulating the restoration of the functional activity of the skin barrier.

OBJECTIVE — evaluate the possibility of using a cream with 5 % filagrinol («Admera») in children (0–18 years old) as basic care in AtD and receive objective data of skin hydration in use, including the rash area, together with glucocorticosteroids.

MATERIALS AND METHODS

There is an open interventional study in parallel groups. The study involves children aged 0–17 years old with atopic dermatitis in the acute stage. The original data are presented in Table 1.

The intervention. The study lasted 14 days. All the participants underwent a clinical examination and evaluation of atopic dermatitis severity, then they were randomly divided into 2 groups: group 1 received tGCS (methylprednisolone aceponate) 1 time daily on lesions + the cream with 5 % filagrinol on skin areas without rash twice a day; group 2 — the same treatment + the cream with filagrinol 5 % applied from day 5 on the lesions additionally to topical corticosteroids. Parents were recommended to apply emollient on the skin 30–60 min after corticosteroid in the evening and without steroid in the morning.

Patients and (or) their parents were explained the rules for applying emollient, its frequency, after which patients under 9 years received 300 ml of the cream for 14 days and older patients received 450 ml.

The patients were randomized by the method of consecutive number assignment. Next, even numbers in the row were included in group 1, odd — in group 2.

Evaluation of atopic dermatitis severity was conducted clinically using international validated scales by standard procedures: evaluation of dermatitis severity on a research-physician's scale (Investigators Global Assessment, IGA); lesion area (Body Surface Index, BSI) and valuation of skin lesion severity in AtD (Eczema Area and Severity Index, EASI, including the assessment of erythema, seals, scratching and rash lichenification, considering lesion area of each body zone). Additionally, the scale of itch severity and patient-oriented eczema measurement (The Patient Oriented Eczema Measure, POEM) were evaluated before and after the intervention. The questionnaire is design for self-completion and (or) filling in by parent/legal representative. It was suggested to choose one of the answer options for each of 7 questions below, then there was the total score calculation by the standard method. The questions of skin dryness and itching were particularly assessed.

Table 1. **Clinical characteristics of the study population**
Таблица 1. **Клинические характеристики исследуемой популяции**

Signs	Value	Notes
Patients Total Completed the study	 72 people 65 people	
Median age	6 [3,75; 7,0] years	min 8 months, max 17 years
Race	Europeans	
Debut of atopic dermatitis (by age): up to a year 1–3 years from 3 years after 7 years	 42 people (60,0 %) 14 people (20,0 %) 10 people (14,3 %) 4 people (5,7 %)	 2 patients had no data on their debut
Form of dermatitis skin lesion area < 10 % skin lesion > 10 %	 55,7 % 44,3 %	
Nature of disease: persistent acute frequent acute rare acute	 11 people (15,7 %) 33 people (47,1 %) 26 people (37,1 %)	
Connection of exacerbations with food allergy (parents' opinion)	54,3 %	
Itching presence (parents' opinion)	85,7 %	
Combined with allergic rhinitis and asthma	54,3 %	
IGA baseline estimate, median	2 [2;3]	
EASI on screening, median	11,5 [6,0; 17,0]	

The strength of nocturnal and daytime itching was rated on a 10-point numeric rating scale — the most severe itch rating scale (Numeric Rating Scale, NRS). The questionnaire is a visual analog scale score from 0 to 10, where 0 points correspond to the absence of itching and 10 — maximum strong sensation. The study measured nocturnal and daytime itching a week before its beginning. Itching was evaluated by guardians of a child.

There was hardware measurement of skin hydration. Videodermatoscopy was conducted using a device in conjunction with accessories for moisture determination by measuring electrical conductivity of keratinocytes. ASW apparatus (Aramo Smart Wizard) and accessories were used in the study to diagnose skin (dermatoscopy) and hair (trichoscopy) under magnification. The study applied the embodiment of ASW-100 and X30 lens with a built-in moisture meter and Wizard software, version 0.19. The principle of the method: the moisture content in the surface layer of the skin is quantified by the passage of electrical current. Electrical conductivity and current between sensor probes, touching the skin surface, are measured and converted into digital form for further evaluation. The higher moisture content in keratinocytes, the higher electrical conductivity rate. Recording of the results was held in the apparatus units.

To study skin hydration with no rash signs, 3 moisture measurements were taken in the right forearm area on the front side below cubital fossa using the apparatus. The average index was put up on the Table.

The sensor was placed in the most severe lesions to measure hydration in the rash area. Other things being equal, the preference was given to the cubital fossa on the right. The measurements were carried out, using the same method. In all these cases moisture measurement of unaffected skin and the one in the rash area was taken before therapy and at the second visit in 14 days.

Satisfaction evaluation of the cream organoleptic properties was conducted using a questionnaire survey where the patients and their parents were asked to answer a number of questions and assess acceptability of using the cosmetic product on the 5-point Likert scale: from 5 (excellent) to 1 (unacceptable). In case of any adverse events,

Table 2. **Composition of the investigated product**
Таблица 2. **Состав исследуемого продукта**

Composition, components: Aqua, Filagrinol*, Glyceryl Stearate/PEG-100 Stearate (Arlacel 165), Cyclomethicone, Glycerol, Niacinamide, Polyamide-5, Sorbitan Monostearate, Cetylalcohol, Hydroxypropyl Bispalmitamide MEA (Ceramide PC 104), 18-beta Glycyrrheticacid, Phenoxyethanol, Sheabutter, Sodiumcitrate, Aloebutter, Citricacidmonohydrate, Cocoabutter, Mangobutter, Disodium EDTA, Zincoxide, BHT, Sweet floral fragrance. * — the stated percentage of filagrinol 5 %.

they were recorded on the second visit; information about the speed and response connection with the cream use as well as the intensity of adverse effect was collected at the same time.

Exclusion criteria were: the presence of moist or infected skin areas, covering significant part of body surface; diffuse form of atopic dermatitis when the use of emollients is not indicated; severe atopic dermatitis; the use of other emollients to exclude a possible combined effect and the inability to objectively evaluate the test product; acute infectious diseases, other skin processes.

The test cosmetic product: "Admera" — a cream for dry and sensitive body skin for children 0+ and adults (manufacturer Dr. Reddy's Laboratories Ltd., India). The certificate of state registration: R.000861.04.22. Approved by Federal Regulatory Organization "Moscow Centre of Hygiene and Epidemiology", expert opinion № 77.01.12. П.003423.11.19 от 15.11.2019 г. The composition is presented in Table 2.

Statistical analysis. All the results were checked for normality and variance equality using Shapiro-Wilk's criterion. Data are unevenly distributed in the study. The Mann-Whitney test was applied for 2 independent samples, the Wilcoxon test was used for paired measurements. If there were more than 2 groups, there was modified analysis of variance for nonparametric data — the Kruskal-Wallis test, for paired measurements — the Friedman test. The analysis was carried out in the graphical shell for the language R (4.1) — Jamovi 2.3 *.

STUDY LIMITATIONS

14 days may not be long enough for a full-fledged evaluation of the skincare product efficiency. We believe that an increase in terms of applying emollients will enhance long-term skin hydration. 2-week period is chosen as a typical interval in routine clinical practice, during which the doctor treats the patient. For ethical reasons, there was no isolated comparison of the effectiveness of steroid cream and emollient in relieving exacerbations in childhood. The patients received the cream and used it at home; correct application and the cream amount on the skin cannot be precisely controlled.

RESULTS

The study was initiated in 72 children, aged from 8 months to 17 years, and completed in 65 patients; 7 patients did not attend the follow-up visit.

"Atopic dermatitis" was diagnosed clinically under generally accepted Hanifin and Rayka criteria and the definition in the position article of the Association of Pediatric Allergists and Immunologists of Russia [1, 9, 11].

The median age of the patients was 6 years with interquartile interval [3,75; 7,0] years that reflects an uneven age composition of children with AtD. Our study involved 2/3 patients under the age of 7, however, there were no differences in gender and race.

Atopic dermatitis was manifested in children in different age periods and had unequal severity according to actual clinical practice and health-care facility attendance. Up to 1 year dermatitis appeared in 60 % of the patients, aged 1–3 years — 20,0 %, aged 3–7 years — 14,3 % and over 7 years — 5,7 % of the children.

The patients were divided into relatively equal groups in accordance with atopic derma-

* The jamovi project (2022). *jamovi*. (Version 2.3) [Computer Software]. Retrieved from https://www.jamovi.org. R Core Team (2021). *R: A Language and environment for statistical computing*. (Version 4.1) [Computer software]. Retrieved from https://cran.r-project.org (R packages retrieved from MRAN snapshot 2022-01-01).

Table 3. **Change in the severity of dermatitis according to IGA criteria within 14 days**
Таблица 3. **Изменение степени тяжести дерматита по критериям IGA в течение 14 дней**

Severity/points	Visit 1, %	Visit 2, %
Clear skin — 0	0	10,5
Almost clear skin — 1	13,0	42,1
Mild severity — 2	50,7	42,1
Moderate severity — 3	34,8	5,3
Severe — 4	1,4	0

$p < 0,001$.

titis severity: 55,7 % had skin lesion area < 10 % and 44,3 % — skin lesson >10 % . The patients with the diffuse form were not included in the study as the use of emollients in the first days of severe skin process increases the risks of skin infection. Age and form of the course were connected. The younger patients experienced more frequent incidence of dermatitis with skin lesson >10 % . The mean age in the children with this form of dermatitis was 4 years, on the contrary, in the group with a skin lesion area < 10 %— 7 years with a significant difference 3 (CI 95 %: 1; 4) years, $p < 0,001$.

Persistent and frequent exacerbations (almost without remission periods and clear skin) were noted by 15,7 % of the patients, exacerbations more than 3 times a year — 47,1 % of the patients and rare ones were observed in 37,1 % of the children. The children with a skin lesion area < 10 % experienced long-tern persistent rash ($p = 0,009$) significantly more often that may be related to low patients' adherence to the treatment of their skin process.

According to the parents, exacerbations were associated with food allergy in 54,3 % of the children and 45,7 % of the patients with atopic dermatitis did not note it.

Itchy skin is a mandatory symptom of dermatitis, however, young children cannot tell about their feelings and complaints. According to the parents, 14,3 % of the children had no itching. The vast majority of the guardians (85,7 %) noted that the children experienced skin itch of various intensity.

Concomitant respiratory diseases such as allergic rhinitis and (or) asthma were observed in 54,3 % of the children; food allergy, according to the parents, occurred in 42,9 % of the patients.

OBJECTIVE CRITERIA OF EFFICIENCY

Dermatitis severity was scored on IGA (Investigator Global Assessment) scale to unify on visits 1 and 2. Before the therapy the patients' IGA ranged from 1 to 4 points. The study involved only children with exacerbation, there was no initial rating "0 — clear skin". Mild and moderate atopic dermatitis was evaluated in most children before the therapy: from 1 to 3 points according to the international scale IGA *.

After 14 days of the therapy 52,5 % of the children had an almost clear skin and a clear skin (IGA 0-1) and 42,1 % — IGA 2 that corresponds to mild dermatitis. The differences between the values in the columns of Table 3 below are reliable ($p < 0,001$).

Analysis of the therapy effectiveness in the groups, divided by the method of applying emollients in the lesion: GCS as monotherapy and GCS + emollient; according to IGA evaluation, there were no differences recorded by the end of the study.

The comparison of the average IGA index before and after the therapy showed a significant reduction in the severity of the disease within 14 days. the mean value in the overall group of patients (median and quartile) before applying the drug was — 2 [2; 3], there was a significant reduction in the mean value up to 1 [1; 2] points on visit 2 . Ranked pair W-test showed differences in values: during the therapy the researcher's evaluation decreased ($W = 406$, $p < 0,01$). The mean difference was 1 point (CI 95 %: 1; 1,5). The

* http://www.consultant.ru/document/cons_doc_LAW_394073/8cae74d5aeedea41504bd85c47c22f0eb62d7b08/

rate of the effect during the therapy was 1,0 — a great effect.

Severity of dermatitis in our sample did not affect the dynamics of rash enhancing during the therapy. Standard scheme with tGCS + emollient led to condition improves in both groups, on average, by 1 step within 2 weeks between visits. Scores declined in the groups: from 2 to 1 vs from 3 to 2 points (p = 0,35). After the therapy, the difference in dynamics and speed of improving the disease course among the children with a skin lesion area < 10 % and >10 % was not found.

Objective evaluation of the severity of the skin lesion generally correlated with the researcher's clinical assessment.

Rash areas decreased under anti-inflammatory therapy: mean BSI indices before treatment were 17,5 % [10,0; 26,8] with the range from 2–54 %. After the therapy the rash area decreased and averaged 3,5 % [1,25; 6,0 %]. Median difference by the rank test had the value 14,5 % (95 % CI: 12,5; 16,5 %), p < 0,001.

EASI index showed the following results. The value distribution was different from parametric one. Values widely ranged from 3 (mild dermatitis) to 35 (severe from with skin lesson >10 %). Most patients experienced a mild and moderate form of AtD. EASI median on visit 1 was 11,5 [6,0; 17,0] points.

After steroid therapy combined with emollient to dry skin, indicators decreased significantly and were 2 [1; 3,8] points on visit 2. Dermatitis severity after the therapy mainly corresponded to a mild course. W rank test shows a significant mean difference in 9 points (95 % CI: 7,9; 10,2), p < 0,001. The rate of the treatment effect corresponds to the strong one that is consistent with literate data — steroid hormones in acute dermatitis have a high degree of efficiency and evidence.

In the study itch was rated by parents on a 10-point scale. The study included maximum rate over the past week. Nocturnal and daytime itching was rated separately. Itching in atopic dermatitis is caused by inflammation in the affected areas and skin xerosis. Parents have difficulties in dividing causes of itching, so a comprehensive single evaluation of itching sensation was used in their survey.

The median of nocturnal itching before the therapy in the general group was 3 [1; 7] with

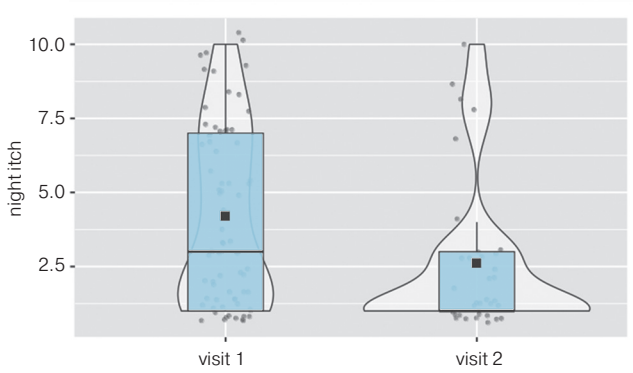

Fig. 1. **Comparison of the assessment of night itching at visit 1 (screening) and after 2 weeks of observation, p < 0,001**

Рис. 1. **Сравнение оценки ночного зуда на визите 1 (скрининг) и через 2 недели наблюдения, p < 0,001**

a significant decline after GCS therapy and the use of emollient up to 1 [1; 3] point. The resulting pair medians were 4,5 and 1 point, respectively, with the mean difference 3 points (CI 95 %: 2; 4). The rate of statistical effect was 0,86 that corresponds to a high impact effect on traits, p < 0,001 (fig. 1).

The median of daytime itching is scored by a similar methodology was 4 [3; 7] points in the general group on visit 1 vs 2,5 [1; 4] points on visit 2. Ranges of rate fluctuations were roughly equal, however most children showed a significant itching dynamics due to the use of the topical therapy. Rank mean difference was 2,26 (CI 95 %: 1,5; 3,0). Effect rate — 0,72 — moderate.

Regardless of the form of atopic dermatitis (with a skin lesion area < 10 % or >10 %), associated with allergic disease or without it, the therapy was effective. Itching decreased during the therapy in the children both with a skin lesion area < 10 % and >10 %.

POEM scale (Patient-Oriented Eczema Measure). Patient-oriented scales are an important way of assessing dermatitis influence on a patient and a person's perception of their pathology. On screening in the general group POEM median was 12 [8; 15] points that corresponds to moderate atopic dermatitis. After the therapy POEM significantly declined up to 4 [2; 9] (mild AtD) with mean difference — 7 [CI 95 %: 4,5; 9].

Analysis of the subgroup by the method (applying emollient in the lesion) POEM did not

Table 4. **Distribution of answers to question No. 7 of the POEM scale about dry skin**
Таблица 4. **Распределение ответов на вопрос № 7 шкалы POEM о сухости кожи**

What is your number of visit?	Respondents	0 days	1–2 days	3–4 days	5–6 days	Every day	none	Total
Screening, visit 1	Observed	2	4	6	7	50	2	69
	% in line	2,95	5,8	8,7	10,1	72,5	2,9	100,0
Visit 2, after applying the cream “Admera”	Observed	21	18	6	4	11	21	60
	% in line	35,0	30,0	10,0	6,7	18,3	35,0	100,0

affect the difference in self-evaluation and dermatitis perception in the children of the studied group: that used GCS on the affected areas as well as group 2 that used GCS + Admera, p = 0,70. In combination therapy POEM indicators decreased in both samples. Co-administration of tGCS and emollient showed its efficiency in the therapy of atopic dermatitis.

It is obvious that POEM scale allows to evaluate emollient efficiency regarding patient’s subjective perception of their xerosis. Respondents are asked to rate dry skin in question 7: “How many days over the past week was your/your child’s skin dry or rough due to atopic dermatitis?” The study could show that the use of the cream with 5 % filagrinol significantly increased the amount of days with no dry skin in the children, reported by their parents. By the second visit 65 % of the patients noted the improvement (skin was not dry or was 1–2 days a week), compared to 9,6 % of the ones, having given the same answer initially. Differences between data were received with high confidence (p < 0,001) (table 4).

POEM rate in the group of children with skin lesion area < 10 % was lower than in the one with skin lesson >10 % (Me 10 vs 13,5, p = 0,031). The children’s parents evaluated skin lesion area < 10 % as a mild form, despite frequent relapses in this group.

Differences in POEM rate were not found in two patient groups, divided over the use of emollient and steroid in rash area (p = 0,52).

Skin hydration (hardware measurements)

The study examined skin hydration while using “Admera” cream and the possibility of combining the cream and topical glucocorticosteroids, including in the lesion. In the study of water content indicators were measured before the therapy and emollient administration (Table 5).

Hardware measurement of skin hydration without rash

Skin hydration out the lesion fluctuated in the range of 29 units: from 4 to 33 units. The mean value in the general group was 8 units with an interquartile range [6,0; 12,0] units. The graph and statistical table show that about 2/3 children have hydration less than 12 units. There is a small number of participants with abnormally high hydration; probably, it is a special clinical variant of dermatitis. The issue requires further study.

The study did not find any dependencies between dermatitis, skin hydration in rash area and the area of dry skin (p > 0,05 in all cases, nonparametric Kruskal-Wallis test):

- time of dermatitis onset;
- child’s age;
- AtD with skin lesion area < 10 % or > 10 % ;
- alleged connection between exacerbation and an allergen;
- presence of skin itching according to parents;
- association with food allergens;
- presence of concomitant respiratory allergic diseases and food allergy.

Perhaps, a relatively small size of samples did not allow to show dependence between the indicators, or processes of inflammation and skin barrier disorders, specific to the external endotype of atopic dermatitis, are stable and do not depend on the factors mentioned above.

In the area of dry skin without rash where glucocorticosteroids were not applied, the hydrating effect was associated exclusively with the emollient use. After 14 days of its use there was a significant increase in the average hydration score: the median in the groups rose from 8 to 10 units,

Table 5. **Summary descriptive table of skin hydration, n=65**
Таблица 5. **Суммарная описательная таблица увлажненности кожи, n=65**

	Skin, screening (visit 1)	Skin, visit 2	Rash, screening (visit 1)	Rash, visit 2
Average	10,0	12,2	9,09	12,8
Standard deviation	6,22	6,75	4,73	6,74
Range	29	31	22,0	30,0
Minimum	4	4	4,00	6,00
Maximum	33	35	26.0	36,0
Shapiro-Wilk, W	0,746	0,803	0,818	0,854
Shapiro-Wilk, p	<0,001	<0,001	<0,001	<0,001
25th percentile	6,00	8,00	6,00	8,00
50th percentile	8,00	10,0	8,00	12,0
75th percentile	12,0	15,0	10,0	15,0

the mean difference 2,5 U (CI 95 %: 5,5; 0) with a small effect size 0,39. The use of nonparametric particulate analysis for Durbin-Conover pairwise comparison provides test statistic lower than the critical level, p = 0,017 (fig. 4).

Hardware measurement of skin hydration in the lesion

In the general group at the 1st visit hydration in rash lesion was, on average, 8 [6; 10] units that did not differ from the forearm skin hydration without signs of inflammation (8 [6; 12]), p = 0,76. After the use of corticosteroids in rash area, the average indictors of hydration rose from 8 [6; 10] to 12 [8; 15] units. Differences between repeated measurements were reliable. The Wilcoxon rank test showed a significant increase of hydration of 4,00 points (CI 95 %: 6,0; 2,0) with a size effect 0,67 (middle), p = 0,001 (fig. 5).

The study investigated the of adding the emollient to GCS in the lesion. The duration of combination therapy (emollient + steroid) in the lesion was 9 days, the total duration is 14 days. The emollient addition on day 5 of therapy did not significantly change the skin hydration by day 14 of monitoring, compared to GCS application on rash area separately.

However, there was a clear positive trend, manifested in the median growth of hardware rash hydration. In group 1 where only methylprednisolone aceponate was used once a day, the hydration median was 10 [6; 15] compared to group 2 that additionally applied the emollient, where it was 12 [8; 15] U, p = 0,59. It might be associated with a short period of using the emollient on the affected skin area. The graphs of the mean comparison and density of the values distribution are presented in fig. 2. There is a slight increase in indicators.

The data shows that there is a tendency for increasing skin hydration with GCS + emollient when used together, however, this dependence is weak. The use of modern nonfluorinated steroid — methylprednisolone aceponate, being a prodrug, with a short course leads to sufficient growth of skin hydration and the inflammation relief and, apparently, does not allow to develop adverse effects on the skin, for at least 2 weeks. The emollient adding did not result in negative outcomes and even allowed to slightly increase moisture content of the skin in the inflammation. Probably, longer courses of the emollient appli-

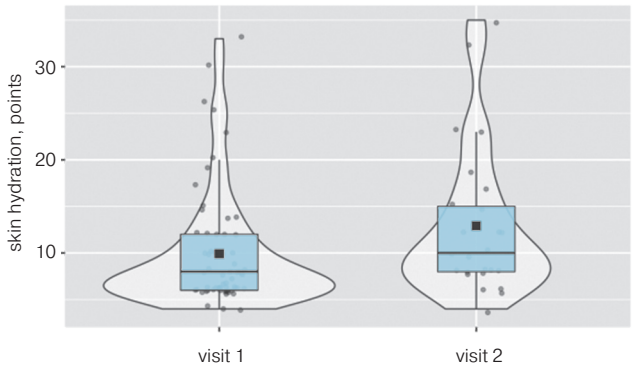

Fig. 2. **Dynamics of the change in hydration at the xerosis site at the 1st and 2nd visits**
Рис. 2. **Динамика изменения увлажненности в месте ксероза на 1-м и 2-м визитах**

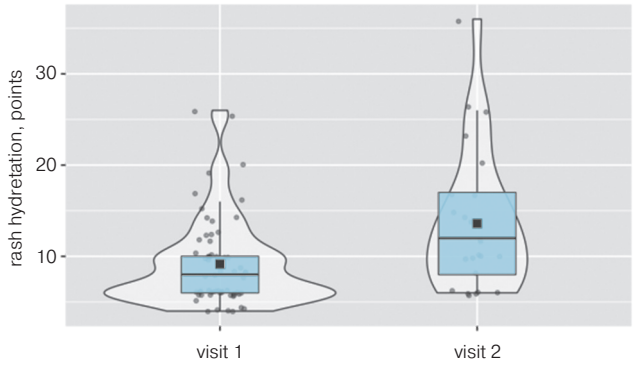

Fig. 3. **Changes in hydration at the rash site against the background of therapy**
Рис. 3. **Динамика изменения увлажненности в месте сыпи на фоне терапии**

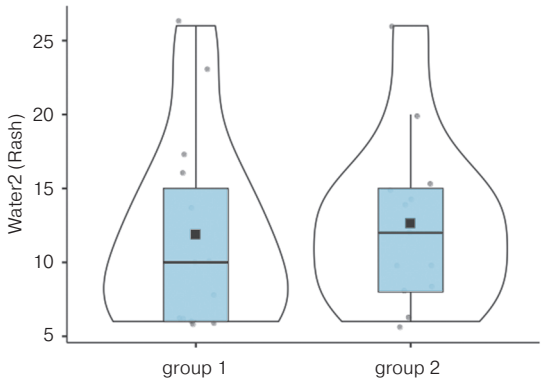

Fig. 4. **Apparent skin hydration in the dermatitis's area after therapy: group 1 — topical corticosteroid; group 2 - topical corticosteroid + cream with 5% filagrinol, p=0.59**
Рис. 4. **Аппаратная увлажненность кожи в области сыпи после терапии: 1 группа — топический кортикостероид; 2 группа топический стероид + крем с 5% филагринолом, p=0.59**

cation are necessary for a reliable implementation of a full hydration effect in the lesion.

Evaluation of organoleptic properties

Organoleptics and tolerance to a cosmetic product are very important for patients and increase adherence to treatment. The emollients are applied at home, it is therefore important patients and their parents to be satisfied with the product quality.

In addition, the questionnaire included questions about the applicability of the cream in actual practice according to patients. Data concerning the cream features and its application to the skin were obtained after 2 weeks of use. Modified 5-point Likert scale was used. Data are presented in Table 6.

Overall rating of the cream, according to the polled, was 4,48 (max 5), "excellent" — 50,8 %, "good" — 46,0 %, "satisfactory" — 3,2 %. It is considered a high rate and ensures the quality of the product.

Ratings "good" or "excellent" for consistency were mentioned by 92,2 % of the respondents. The majority were completely satisfied with absorption rate (100 %) and homogeneity of the cream structure (98,4 %). The patients noted a lack of stickiness (98,4 %) and ease of the product application (98,4 %). High ratings were given to fat content (93,2 %), subjective sense of moisturizing after application (90,5 %) and skin softening (93,5 %). 82,5 % of the respondents had no claims to the dispenser use, 96,8 % — to the tightness and 85,7 % — to the odour.

Subjective evaluations, affecting the overall rating, were obtained on the indicators "odour" and "dispenser convenience". Traditionally, user preferences for these criteria vary. In the interview the patients paid attention to the lack of an dosage pump and mild cream intake during squeezing . For some respondents the odour was neutral and it was noted to be the norm for medical cosmetics. This group of patients notes the inadmissibility of perfume in creams, the other part expects maximum similarity to home care cosmetics and odour from the cream.

Assessment of adverse events with the product application

Given the multicomponent composition of the cream and a frequent association of atopic dermatitis with contact reactions, it was important to evaluate tolerability of the product and the frequency of adverse events with its application. The patients had no complaints about serious adverse reactions after using the cream: nobody experienced specific contact-allergic dermatitis. However, the questionnaire contained direct questions about the development of possible reactions after contact with the skin. All the patients were warned that emollients cause burning when applied on inflammation areas and it was not recommended to use the cream on them. It was not possible to monitor the process of applying the cream at home. Apparently, in some cases,

Table 6. **Evaluation of the organoleptic properties of the product according to the patients**
Таблица 6. **Оценка органолептических свойств продукта**

Indicator	User rating				
	Excellent, %	Good, %	Satisfactory, %	Bad, %	Unacceptable, %
Consistency	68,8	23,7	7,8		
Homogeneity	63,5	34,9	1,6		
Odour	60,3	23,8	11,1	3,2	1,6
Lack of stickiness	68,3	25,4	4,8		1,6
Fat content	56,5	37,1	4,8		1,6
Moisturizing	44,4	46,0	9,5		
Softening	53,2	40,3	6,5		
Ease of application	66,7	25,4	6,3	1,6	
Absorption rate	77,4	22,6			
Dispenser convenience	46,0	36,5	17,5		
Tightness	73,0	23,8	3,2		
Overall rating	50,8	46,0	3,2		

in violation of the doctor's recommendation, the cream entered the affected areas, and some patients noted adverse reactions.

The objective criteria in the form of a rash that the patients' parents directly associated with the cream were noted by only 1,6 % of the polled (1 person), and even in this case, according to the researcher, no convincing evidence of exact connection between the rash and the cream application could be obtained. The other signs were rather subjective. Moreover, due to an early age of most participants that used the cream, their parents were interviewed instead of them. The patients did not decide against the cream and clinical examination did not record any evidence of contact and irritant dermatitis on the children's skin at the second visit. Thus, there was good tolerability and no significant adverse effects when applying the multicomponent cream with 5 % filagrinol that makes it possible to use in children's practice.

DISCUSSION AND OVERALL CONCLUSION

The study can trace the general trends of natural atopic dermatitis evolution, coinciding with the world-wide trends. Unequal age distribution of children with AtD is consistent with literature data and reflects high prevalence of eczema at a young age. Asymmetrical age distribution is caused by a more permeable skin barrier, immunological skin maturation and gradual transition to dermatitis with a skin lesion area < 10 % in teenagers. According to our study and the sources Roduit C, 2017, atopic dermatitis has different phenotypes, depending on manifestation time and a link to food allergy. Early childhood up to 4–6 years is most conducive to the disease development and during this period several clinical AtD variants occur simultaneously: early transient, early persistent and late persistent phenotypes [19]. Possible filaggrin mutations clinically manifest in affecting typical areas of the thinnest and most permeable skin that was shown in the work of Carson C, 2012 [20]. Our study shows the prevalence of dermatitis with a skin lesion area < 10 % is combined with a long course and frequent relapses that indirectly confirms the correctness of the hypothesis about maintaining inflammation in those with the impaired epidermal barrier. Dermatitis localization in favorite areas and the lack of adequate anti-inflammatory therapy increase the risks of prolonged existence of the process even with dermatitis with a skin lesion area < 10 %.

The link between allergic diseases and the combination of dermatitis, rhinitis and asthma is a well-known fact, though strategies of developing allergic diseases ("atopic march'") are constantly reviewed. Without denying this very tendency to the systemic T2-inflammation, it should be noted that the presence of all march stages is recognized not mandatory, however, it is becoming a certainty that defects in the FLG gene, respon-

sible for filaggrin synthesis, are associated with an increased risk of asthma development [21]. Therefore, it is interesting to use emollients that contain stimulants for the synthesis of epithelial barrier components, such as filagrinol, and to study the influence of emollient-plus on the dynamics of sensitization development.

There was no analysis of the patients' medical history that participated in our study on the association with food allergy; sensitization and its role in the development of exacerbation was not considered in the study. Traditionally, parents are convinced that dermatitis is mostly related to allergies. Analysis of the link between sensitization and exacerbations of atopic dermatitis was previously conducted on the basis of the Moscow Scientific-Clinical Consultative Center of Allergology and Immunology, which showed that there is a high frequency of food allergy and dermatitis association at an early age up to 2 years [22]. Parents' opinion that food allergy is a common trigger of AtD at an older age should be treated with caution as the results of a large meta-analysis suggest the opposite. Parents are convinced that up to 30 % of the population have food allergy, in the case of studying sensitization (laboratory or skin tests) the frequency of food allergy drops to 10–15 %, and with provocative tests does not exceed 3–5 %, even in cohorts from the United Kingdom and Australia where the frequency of food allergy is traditionally high [23].

The prevalence of mild and moderate forms are reflected in the structure of patient visits to the center. The study included only children with acute atopic dermatitis: 50,7 % of the children had a mild form (IGA = 2), 34,8 % — a moderate from (IGA = 3). After 2 weeks clear skin (IGA = 0) was observed in 10,5 % of the patients. 42,1 % of the patients had almost clear skin (IGA = 1), mild severity is reported in 42,1 % of the children, IGA = 3 — in 5,3 % of the patients. EASI rates and lesion areas were moving in the same direction. It is obvious that within 2 weeks the therapy evaluation moved by 1 point: mild forms moved to almost clear skin, moderate forms improved to mild ones. Reduction in the final IGA, EASI, BSI score against the backdrop of the therapy is achieved by the combined effect of GCS and the emollient that does not allow to evaluate the contribution of each agent to remission induction. The traditional therapy regimen, recommended by the European and Russian community, was effective [1, 9, 11].

The dynamics of the itch change was reliable in the study. The study rated nocturnal and daytime itching on NRS scale as maximum over the last week and decreased during the treatment. By the end of the study 3/4 of the patients had the itch median <4 and 50 % — less than 1 point that is considered an excellent indicator of the therapy effectiveness. Limitations of this result lie in the understanding that itching was noted both in the inflammation areas where steroids were applied, and xerosis ones. For ethical reasons, the authors could not leave the patients without both the moisture therapy and topical steroids. The study conclusions of the leading role of emollients in the aspect of general itching relief should be treated with caution. However, the positive effect of emollients on itching in dermatitis has been repeatedly shown earlier and this postulate does not require proof [24].

The main study result is the evidence of a reliable influence of the cream with filagrinol on skin hydration both in rash and dry skin areas that is manifested in a meaningful change of patient satisfaction with the condition of their skin. It is obvious in the positive dynamics of the patients' responses concerning dryness after using the emollient, assessed by the validated POEM questionnaire.

The mean values of skin hydration increase (median difference to the baseline), when measuring with videodermatoscopy out the lesion in the general group, was approximately 31,25 %. In the dry skin area without rash, where topical glucocorticosteroid was not applied, the moisturizing effect was associated exclusively with the use of the emollient. These values were confirmed by the data of another Russian research of 12-week application of "Admera" cream in children with mild and moderate atopic dermatitis. The level of skin hydration in the research was measured by transepidermal water loss (TEWL) index. TEWL average in the screening was 10,95 g/m2/h, though by the second visit in 2 weeks it decreased up to 9,033g/m2/h, (p <0,001), That trend was seen throughout the follow-up period. By day 84 TEWL mean value was 4,433g/m2/h (p <0,001). Thus, the cream with filagrinol has

been proven to have a significant effect on the level of skin hydration, including the patients without administered topical glucocorticosteroids as part of therapy [18]. The rates of skin hydration change for the cream with 5 % filagrinol "Admera" are not inferior to the results, given in the literature for similar products. In Bergera-Virassamynaïk S.et al (2023) study the transepidermal water loss index by day 28 of applying the emollient decreased by 24 %. the comparison has limitations as different devices and methology for measuring were used, and different areas of the skin were measured: there is the forearm skin in our study and skin of the eyelids in Bergera et al. research. However, the overall trend in the use of emollients is evident. The use of the emollient of a new generation gives patients a significant benefit [25].

The mean values of increasing skin hydration in the affected areas in the general group, calculated using the same method (median difference 4, reference value 8 U), amounted to solid 50 %. It shows that hydration directly depends on inflammation level in the lesion. In our study such moisturizing effect is accomplished by local application of modern steroids — methylprednisolone aceponate, though there are studies when systemic drugs, such as dupilumab, reduced the level of transepidermal water loss [26]. Local use of fluorinated drugs hormones, on the contrary, leads to high incidence of side effects in the lesion, the risk of skin thinning and its depigmentation. The effects are shown for betametazonavaleriat 0,1 % when used twice a day for 4 weeks [27]. Such drugs were not used in our study and hardware measurement of their effect on skin hydration was not carried out.

Studies on the effect of adding the emollient to GCS in the lesion in a short time was conducted in the therapy subgroups. Screening showed median values equal to 8 [6; 10] U in both groups. Adding the emollient on the 5th day of the therapy allowed to have a statistically significant increase in skin hydration by the 14th day of observation, compared to the use of GCS in the rash alone. In group 1, where only methylprednisolone aceponate was used once a day, hydration median increased by 20 % at the 2nd visit, compared to group 2 that additionally applied the emollient and the difference with visit 1 was + 50 %. However, the differences turned out to be unreliable, perhaps, due to small groups and the use of less sensitive long-rank tests, p = 0,59. The joint effect of steroid + emollent was previously shown in small studies, but unlike our study (2 weeks), they generally lasted around 12 weeks [28]. Increasing skin hydration in the lesion when adding the emollient is useful for the prevention of exacerbations and requires further study to compare the effectiveness. Adding new ingredients, e.g. filagrinol, apparently, may provide additional benefits for patients [29, 30].

The analysis regarding patients and their parents/legal representatives' satisfaction of using "Admera" cream for 2 weeks of observation found: overall rating of the cream, according to the polled, was 4,48 (max 5), "excellent" — 50,8 %, "good" — 46,0 %, "satisfactory" — 3,2 %. This is a high rate and indicates the high quality of the product. The study reported no cases of reduction in intent to apply "Admera" as a skincare product.

CONCLUSION

1. Emollients play an important role in treating atopic dermatitis. They decrease the severity of rash and dry skin, and steroids relieve inflammation in the lesion. The use of the cream with 5 % filagrinol ("Admera") together with methylprednisolone aceponate cream for 2 weeks allows to achieve significant regression of inflammation, according to the doctor's (IGA, EASI) and patient's (POEM, visual itching scale) evaluation.
2. Use of the cream with 5 % filagrinol ("Admera") is justified for children with dry skin as the product significantly increases skin hydration, measured by hardware in rash areas and dry skin without dermatitis.
3. Positive trends in measuring skin hydration with the combined use of GCS and the emollient in the lesion for 9 days could not reach a significant level. However, the mean values of the moisture content in the skin increased (20 % vs 50 %) that allows to predict the effect realization with longer use of the emollient.
4. The course of using the modern moisturizer, cream with 5 % filagrinol, for 2 weeks is enough to obtain subjective differences in perceiving dry skin under POEM scale and to prove the increase in skin hydration objectively by measuring the moisture content in epidermis.
5. Consumer properties of the cream with 5 % filagrinol ("Admera") as rated by the parents of the children with atopic dermatitis детей and allergic diseases, corresponds to "good" and "excellent" in most cases with average values 4,48 in the general patient group. The cream can be recommended for use by children aged 0–18 years with dry and atopic skin as well as patients with proven allergic sensitization to moisturize dry skin in areas with no rash and combined with topical glucocorticosteroid on the 5th day of the disease after relief of acute inflammation.

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