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Double-blind controlled randomised study of lactulose and lignin hydrolysed combination in complex therapy of atopic dermatitis

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Background: Atopic dermatitis (AD) is an immune mediated disease with complex pathogenesis characterised by persistency, frequent exacerbations, and inefficacy of existing therapies. Damaged or weakened intestinal microbiocenosis is considered as an important aetiological factor of AD. The aim of this study was to evaluate the efficacy and safety of medical preparation Lactofiltrum (lactulose and sorbent (lignin hydrolysed)) in comparison with placebo in complex with standard therapy of AD.

Methods: Double-blind, placebo controlled, randomised comparative study of effectiveness and safety of 400 mg lactulose and 120 mg lignin hydrolysed combination as a part of standard combined AD treatment, conducted in parallel groups of patients aged 18–60.

Results: Comparison of clinical efficacy of Lactofiltrum in combination with the standard treatment has been demonstrated by measuring the following parameters: administration of Lactofiltrum results in 1) distinct clinical improvement in 56.75% of patients, 2) decrease of the mean values of scoring atopic dermatitis (SCORAD) index in 71.94% of patients, 3) elimination of itching in 50% of patients, and 4) life quality improvement for 76.41%. In the placebo group, 1) distinct clinical improvement was observed in 20% of patients, 2) decrease in SCORAD index values observed by 56.98%, 3) itching relief in 15.56%, and 4) life quality improvement by 36.38%.

Conclusions: Clinical improvement and persistent termination of clinical symptoms provide evidence of effectiveness in use of Lactofiltrum combined with the standard treatment of AD.

Keywords: *atopic dermatitis*; *Lactofiltrum*; *lactulose*; *lignin hydrolysed*; *allergic disease*

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Atopic dermatitis (AD) is a chronic inflammatory skin disease. Aetiology of the disease is associated with genetically determined individual sensitivity to allergens, and with exposure to unfavourable environmental factors, social status of the patients, and presence of comorbidities (1). The main pathogenetic mechanism in the development of AD is disruption of the genetic control of basic IgE level or its receptors, which leads to development of an immune reactions cascade, with impaired differentiation of T-lymphocytes (with a predominance of T-suppressors), changes in cytokine profile, and development of allergic skin inflammation within overall sensitisation (2, 3). Damaged or weakened intestinal microbiocenosis is considered as one of the most important aetiological factors of AD (4). Pathology of the gastrointestinal tract (GIT) largely determines the severity of AD (5, 6).

The therapy is aimed at restoring balance of intestinal microflora, as well as at the removal of toxic allergen substances, in combination with basic anti-inflammatory AD therapy can render positive influence on the course of disease (7).

Bifidobacterium and *Lactobacillus* are the basis of both primary colonic normal microbiocenosis formed in healthy newborns in the neonatal period, and of normal microflora in adults of all ages. The most important function of Bifidobacteria and Lactobacilli in host is to provide colonisation resistance by participation in metabolic processes. Because of its immunostimulatory function normal microflora is able to enhance activity of natural killer cells, as well as to activate synthesis of secretory immunoglobulins, interferon, and various cytokines (8–11).

Most frequently, six species of *Lactobacillus* are allocated in human biotope: *L. salivarius*, *L. acidophilus*,

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L. casei, *L. plantarum*, *L. fermentum*, and *L. brevis*. Lactobacilli actively compete with potential pathogens for the limited nourishing substrates and adhesion places on epithelium; they also stimulate the activity of the host immune system (12).

Bacteria cannot usually colonise the colon irreversibly. Therefore, a rational approach to counter pathological changes in intestinal microflora (for prevention or treatment) is to support the growth of existing intestinal microflora that is physiologically adequate to the human organism.

It is presumed that the use of prebiotics may have an impact on the immune system, both directly and indirectly, as a result of intestinal fermentation and promotion of the growth of certain members of microbiocenosis of the digestive tract. It helps stimulating the synthesis of short-chain fatty acids (intestinal forms associated with lymphoid tissue) that can have influence on immunomodulation, because of the ability to increase production of IL-10 and TGF-β1, which are anti-inflammatory cytokines, and play an important role in reducing allergen-induced responses (13, 14). IL-10 binds with specific receptors on intestinal epithelial cells and regulates their participation in inflammation and immune response in the GIT. IL-10 may also prevent IFN-γ induced disruption of the colon epithelial barrier, which impedes endotoxemia. Recent studies have shown that consumption of various prebiotics promoted increased production of IL-10 (15–18).

Therapy aimed at restoring the balance of intestinal microflora and removal of toxic substances combined with basic anti-inflammation therapy of AD may have positive influence on the course of the disease.

Lactofiltrum which is considered as combined medical preparation (lactulose 400 mg, lignin hydrolyse 120 mg, tablets; AVVA RUS JSC) used both of these strategies including lactulose as prebiotic and lignin hydrolysed as enterosorbent. Lactulose is a synthetic disaccharide, whose molecule consists of galactose and fructose. When ingested, lactulose is not digested in the upper GIT and it reaches the colon intact. Lactulose has a positive physiological effect by selectively stimulating the necessary growth and activity of the intestinal microflora (19). Lignin hydrolysed is a natural enterosorbent consisting of hydrolysed wood components and it has high sorption activity and non-specific detoxification effect. It binds pathogenic bacteria and bacterial toxins, medications, salts of the heavy metals, alcohol, allergens, and excess of metabolic products (including bilirubin, cholesterol, urea, and other metabolites, causing endogenous toxaemia) in the intestine so they are excreted from the organism. Lactulose does not sorb on lignin surface as its molecule is small and bears a negative charge on its surface, similarly to active groups of lignin (20, 21).

The aim of this study was to research the efficacy and safety of use of Lactofiltrum in the combined therapy of AD.

Materials and methods

Trial design

The total design was a double-blind placebo controlled randomised comparative study in parallel groups of patients with a diagnosis of AD, based at the Clinical Centre of Moscow State University of Medicine and Dentistry, at the Department of Skin and Veneral Diseases, and at Clinical Centre 'Dermatology and Venerology Clinical Dispensary No. 21 of Moscow Health Department'. To monitor the progress of study participants, follow-up visits were conducted on study days 10, 21, and 30 after treatment.

Participants

The study included 89 patients with AD (30 women [33.71%] and 59 men [66.29%]), aged 18–60 years, diagnosed with AD in moderate or severe exacerbation, according to specific criteria for the diagnosis of AD according to Hanifin and Raika (1), scoring atopic dermatitis (SCORAD) index >25 (medium and severe) based on objective (intensity and prevalence of skin lesions) and subjective (intensity of day itching and sleep disturbance) criteria.

All patients were randomised into two groups, depending on the treatment:

Group 1 (Lactofiltrum) ($n=44$) – patients receiving standard therapy (antihistamines, topical steroids) in complex with Lactofiltrum medication (lactulose 400 mg, lignin hydrolysed 120 mg) – two tablets, three times a day for 21 days.

Group 2 (control) ($n=45$) – patients receiving standard therapy (antihistamines, topical steroids) in complex with placebo – two tablets, three times a day for 21 days. The placebo contained sodium croscarmellose (4%), magnesium stearate (1%), dye 'Caratom BS-7' (1%), and microcrystalline cellulose (94%).

Therapeutic effect was assessed on study days 10, 21, and 30 after treatment.

Subjects with professions associated with increased risk of skin trauma, hypothermia, sun exposure, and exposure to ultraviolet radiation were excluded. Additional exclusion criteria were the following: any severe, decompensated or unstable somatic diseases or conditions that threaten the patient's life or impair the prognosis of the disease (anaemia, diabetes); other related diseases which require the appointment of systemic corticosteroids, cytotoxic drugs, immunosuppressants, anti-metabolites, anticytokine drugs and/or local therapy during the study (parasitic diseases, diffuse connective tissue disease, lymphomas of the skin, lymphoma, scabies, lichen planus, psoriasis); pregnancy and breast-feeding; usage of sorbents, pre- and probiotics within 2 weeks before the study; acute psychotic positive symptoms (psychosis, hallucinations, delusions); and usage of antipsychotics and tranquilisers within 2 weeks before study.

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Efficacy assessments

Each of the six objective signs (erythema, oedema/papular elements, crust/wet, excoriation, lichenification/exfoliation, dryness of the skin) was evaluated on 4-level scale: 0 = absent, 1 = weak sign, 2 = moderate, 3 = strong. Prevalence of skin lesions was assessed by the rule of 'Nine', where palmar surface of hand is adopted as unit. Total amount is rounded up to 5 points and may be from 0 points (no skin lesions) to 96–100 points, when skin is fully affected. Each subjective symptom was evaluated from 0 to 10 points and the scores were summed. Total score of subjective symptoms may range from 0 to 20.

Intensity of pruritus was assessed with the 5-point behaviour rating scale (BRS) (22), which considers degree of discomfort during day and night.

Quality of life was assessed with dermatological life quality index (DLQI) by using special anamnesis questionnaire (23).

Safety assessment

Safety assessment considered results of laboratory blood and urine tests and adverse events if clinically relevant. All adverse events and serious adverse events, occurred during the study were recorded. No clinically significant changes were observed in the laboratory test results, both blood and urine; no allergic reactions or other adverse events were reported.

Statistical methods

Quantitative and ordinal data were analysed and values of arithmetic mean (M), standard deviation (SD), 95% of confidence interval (CI) for mean, median, and interquartile range were calculated for both groups. Distribution of qualitative variables is presented as values of sampling fraction (W), its standard error, and 95% CI for the fraction. For all bilateral statistical tests, threshold alpha error level was set at 0.05.

Consensus and ethics committee approval

Informed consent was obtained from all participants. The Ethics Committee of the Russian Federal Service on Surveillance in Healthcare approved the study protocol. All investigations were conducted according GCP.

Table 1. Dynamics of mean values of SCORAD index in patients as a result of treatment (points)

Visit	Group 1 (Lactofiltrum)	Group 2 (control)
I (baseline)	42.23 ± 11.36	47.77 ± 10.94
II (day10 ± 3)	24.9 ± 8.86	35.94 ± 11.39
III (day 21 ± 3)	11.85 ± 5.56*	20.55 ± 7.77
IV (day 51 ± 3, follow-up period)	4.31 ± 1.58*	13.10 ± 6.34

*$p < 0.05$.

Results

Treatment efficacy was assessed by employing SCORAD index evaluation method. As illustrated in Table 1, SCORAD index' dynamics in Group 1 complex therapy contributed to a significant reduction 42.23 ± 11.36 to 11.85 ± 5.56 points ($p < 0.05$), which makes 71.94%. The control group (Group 2) had a less intensive reduction of SCORAD index, though it was also significant: from 47.77 ± 10.94 to 20.55 ± 7.77 points ($p < 0.05$), which makes 56.98%. Further decline in clinical symptoms in both groups (Group 1: 4.3 ± 1.58 points ($p < 0.05$); Group 2: 13.10 ± 6.34 points ($p < 0.05$)) can be rationalised based on the fact that the study (and the period of observation) was conducted in summer, when patients with AD usually observe spontaneous remission. Nevertheless, it has to be noticed that SCORAD index' dynamics were more intensive in patients treated with lactulose and lignin hydrolysed combination, reflecting anti-recurrence activity of proposed method of treatment.

Upon assessing skin rash disappearance in Group 1, complete disappearance was found in 1 patient (2.27%), excellent improvement in 24 (54.55%), and good improvement in 19 (43.18%); moderate improvement, no improvement, and negative result were not recorded (Fig. 1).

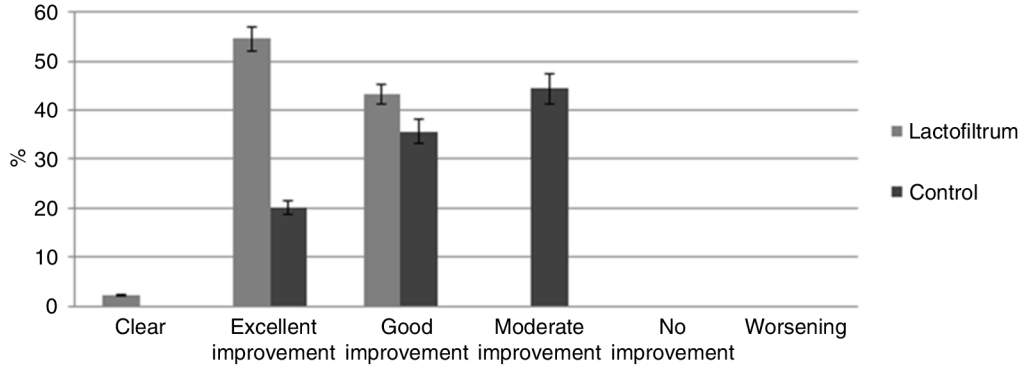

Fig. 1. Skin lesions disappearance as a result of treatment with Lactofiltrum (Group 1) compared to the control (Group 2) on 21 day of treatment.

Table 2. Dynamics of mean values of itching intensity in patients after treatment (points)

Visit	Intensity of day itching		Intensity of night itching	
	Group 1 (Lactofiltrum)	Group 2 (control)	Group 1 (Lactofiltrum)	Group 2 (control)
I (baseline)	2.72±0.63	2.93±0.65	1.35±0.9	1.69±0.11
II (day10±3)	1.44±0.13*	2.13±0.72	0.44±0.15*	1.13±0.12
III (day 21±3)	0.53±0.05*	1.35±0.83	0.05±0.01*	0.58±0.10
IV (day 51±3, follow-up period)	0.12±0.05*	1.18±0.86	0.05±0.003*	0.35±0.09

*$p < 0.05$.

Therefore, skin rash intensity was reduced by more than 75% in 56.75% of patients treated with Lactofiltrum.

Lack of patients with weak positive response or worsening condition is indicative of high efficacy of combined treatment with lactulose and lignin hydrolysed combination in AD patients.

In Group 2 (placebo plus standard course of therapy), efficacy of treatment was lower compared to Lactofiltrum treatment. Full skin lesions recovery was not observed in any of the patients, excellent improvement was observed in 9 patients (20%), good improvement in 16 (35.56%), and moderate improvement in the remaining 20 patients (44.44%). No improvement and negative result were not recorded (Fig. 1).

In Group 1, in an absolute majority of patients (56.75%), skin rash intensity reduction by more than 75% was observed, and no patients showed a weak positive response or deterioration as a result of the treatment. That indicates high efficacy of the combined therapy with lactulose and lignin hydrolysed combination in AD.

Analysis of dynamics in skin itching intensity was conducted according to the BRS scale. As shown in Table 2, reduction in the intensity of pruritus was faster in Group 1. Significant decrease of day itching intensity (from 2.72±0.63 to 1.44±0.13 points ($p < 0.05$)) and night itching intensity (from 1.35±0.90 to 0.44±0.15 points ($p < 0.05$)) was reported after 10 days of treatment. By the end of the treatment, day itching was reported only by 50% of patients in Group 1 (mean BRS score 0.53±0.05) and 4.54% of patients reported night itching (mean score 0.05±0.01). In Group 2, a significant decrease in itching intensity was also reported by the end of therapy: in day itching from 2.93±0.65 to 1.35±0.83 points ($p < 0.05$), in 84.44% of patients; and in night itching from 1.69±0.11 to 0.58±0.10 points ($p < 0.05$). However, it was still reported in 51.11% of patients.

Similar to SCORAD and BRS indexes' dynamics, the most significant DLQI reduction was registered in Group 1.

As shown in Table 3, reduction in DLQI intensity was more significant. After 10 days of treatment, patients in Group 1 reported almost twofold decrease in DLQI and in Group 2 decrease was recorded by approximately 10%. By the end of the treatment, DLQI in Group 1 decreased by 4 times, while at the same time in Group 2 by only 1.5 times.

During the follow-up period, further decrease of DLQI was observed in both groups; however, a month after stopping the treatment, the index was significantly higher in Group 2 than in Group 1. DLQI in Group 1 has decreased by 10 times, whereas in Group 2 only by 2 times.

Based on these data, it can be concluded that use of lactulose and lignin hydrolysed combination in complex with standard therapy for AD improves the quality of life of patients.

Discussion

In patients treated with lactulose and lignin hydrolysed combination as part of combined therapy prolonged treatment efficacy was observed; noticeable clinical improvement was found in 56.75%, elimination of day and night itching in 50%, reduction of SCORAD index values by 71.94%, and quality of life improvement by 76.41%. In the control group, clinical improvement was observed in 20% of the patients, elimination of itching in 15.56%, decrease in SCORAD index value by 56.98%, and life quality improvement by 36.38% (Fig. 2).

Kalliomäki et al. showed that differences in the neonatal gut microflora precede the development of atopy, suggesting a crucial role of the balance of indigenous intestinal bacteria for the maturation of human immunity to a non-atopic mode (24). Thus, in children suffering from AD intestinal lactobacilli colonization occurs less intensively

Table 3. Dynamics of DLQI decrease (points)

Visit	Group 1 (lactulose, lignin hydrolysed)	Group 2 (placebo)
I (baseline)	9.37±5.89	12.89±6.95
II (day10±3)	5.65±4.59	11.07±7.86
III (day 21±3)	2.2±1.03*	8.20±3.42
IV (day 51±3, follow-up period)	0.93±0.04*	6.49±3.14

*$p < 0.05$.

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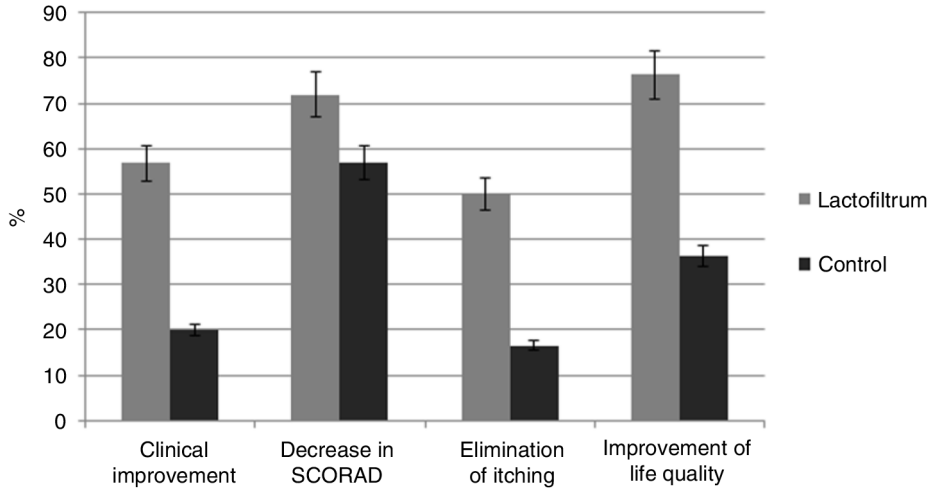

Fig. 2. Efficacy of AD treatment with Lactofiltrum (Group 1) compared to the control (Group 2), in %.

and bifidobacteria titers are significantly lower than in healthy children. This was confirmed in a double-blind randomized trial including 259 infants at risk for atopy that together with significant reduction of incidence of AD in the group receiving mixture of galactooligosaccharides and fructooligosaccharides compared to the placebo group (9.8% vs 23.1%) showed that prebiotic supplements were associated with a significantly higher number of faecal bifidobacteria compared with controls (25). During Lactofiltrum treatment, the prebiotic therapy of AD promotes colonisation of lactobacilli and bifidobacteria and could align the imbalances between species in microbiocenosis.

Administration of Lactofiltrum may lead to restoring of the balance of the intestinal microflora due to the action of lactulose as prebiotic and indirectly affecting the immunological parameters (increase of IL-10 and TGF-β1 production, which, as anti-inflammatory cytokines, play an important role in reducing allergen-induced response) (17, 20). Prebiotics are fermented by probiotic strains which are able to stabilize gastrointestinal barrier function that plays important role at improving atopic dermatitis (26, 27). Effect of prebiotics during AD treatment was confirmed by data from different meta-analysis. Thirtytwo percent reduction in the incidence of AD after using prebiotics has been reported (28). Cochrane (2013) systematic review concluded that dermatological manifestations of allergy are reduced after prebiotic treatment (29).

The second component of Lactofiltrum – lignin hydrolysed – has a high sorbtion capacity, and binds and removes allergens, mediators, products of allergic reaction, metabolites, toxins, and active peroxides compounds from the intestine. It has reparative properties and does not harm intestinal mucosa as it is non-toxic, non-absorbable, and is completely excreted from the intestine within 24 h. The impact of sorbent could enhance the lactulose prebiotic action and lead to weakening and eliminating of AD' clinical manifestations (20, 21).

The content of the placebo includes microcrystalline cellulose which has lower sorbtion capacity according to our data (not shown). The prebiotic effect seems to be negligible compared to lactulose and microcrystalline cellulose often used in study protocols for evaluating of prebiotic effect of test substances (30–32). Hence, significant improvement of symptoms in the placebo group is unlikely attributed to placebo content and possibly could be connected with psychological factors that are difficult to control.

Overall, clinical improvement and persistent termination of clinical symptoms provide evidence of effectiveness in use of Lactofiltrum combined with the standard treatment of AD. Nevertheless, correlation between the reduction in clinical symptoms of AD and immune modulation by influencing pro- and anti-inflammatory cytokines with lactulose and lignin hydrolysed combination is of extraordinary interest and requires further investigation.

Conflict of interest and funding

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