

Efficacy of Probiotic Therapy on Atopic Dermatitis in Adults Depends on the C-159T Polymorphism of the *CD14* Receptor Gene - A Pilot Study

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Abstract

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BACKGROUND: The C-159T polymorphism of the *CD14* receptor gene can be associated with the development of atopic dermatitis. Probiotics can modulate chronic inflammation through activation of the CD14 receptor. So, the efficacy of probiotic therapy can be dependent on this genetic polymorphism.

AIM: The purpose of the study was to investigate the efficacy of adding probiotic (*Lactobacillus acidophilus*, LA-5 and *Bifidobacterium animalis subsp. lactis*, BB-12) to standard treatment (ointment of fluticasone propionate 0.005% and emollient) of atopic dermatitis in adults during 28 days, depending on the stratification of patients on CC or TT genotypes of the *CD14* receptor gene.

MATERIAL AND METHODS: The study included 37 adult patients with AD. There were identified 19 patients with exogenous (IgE-dependent) and 18 with endogenous (IgE-dependent) AD. To evaluate the efficacy of the probiotics all patients were divided into three groups for both exogenous and endogenous AD. The first group was selected from patients with CC genotype (C-159T) who received standard therapy (ointment of fluticasone propionate 0.005% – 2 times a day, emollients – 2 times a day) and probiotic (*Lactobacillus acidophilus*, LA-5 and *Bifidobacterium animalis subsp. lactis*, BB-12 - 1 capsule 2 times per day) The second group included patients with CC genotype, who received only standard therapy. The third group was presented by patients with TT genotype (C-159T) who received standard therapy and probiotic. The SCORAD and DLQI parameters were evaluated on Day 0, 14 and 28. The level of IL-4, IL-5, IL-10, TGF- β cytokines was determined on Day 0 and Day 28.

RESULTS: The results of our study found that the addition of probiotics (*Lactobacillus acidophilus*, LA-5 and *Bifidobacterium animalis subsp. lactis*, BB-12) to standard treatment (ointment of fluticasone propionate 0.005%, emollient) significantly increased the effectiveness of treatment of atopic dermatitis in adults with exogenous form and CC genotype (C-159T), confirmed by clinical (a significant decrease of SCORAD and DLQI indices) and immunological criteria (a significant decrease of IL-4 and an increase of TGF- β).

CONCLUSION: Simultaneous determination of the exogenous or endogenous form, identification of the C-159T genotypes, evaluation of the serum level of IL-4 and TGF- β can serve as an algorithm for the personalised treatment of patients with atopic dermatitis.

Introduction

To date, there are practically no drugs for the treatment of atopic dermatitis (AD) that can modify chronic inflammation or activate natural suppressor immune mechanisms, especially by activating regulatory T-lymphocytes. However, probiotics themselves may have such properties.

Probiotics are living microorganisms that can be of benefit to health when administered in adequate doses [1]. The most commonly used are

Lactobacillus, *Bifidobacterium*, *Enterococcus*, *Propionibacterium* and some yeasts such as *Saccharomyces boulardii*. Their benefit is proven in the treatment of diarrhoea after taking antibiotics, irritable bowel syndrome and inflammatory bowel disease [2]. Genetic polymorphism and the effect of microorganisms on the immune system are closely related to the modulation of skin inflammation in AD, including the activation of the CD14/TLR-4 receptor complex by endotoxin of gram-negative bacteria.

The *CD14* receptor gene is located on chromosome 5q31.1, has two exons and 3900

nucleotides [3]. In the same locus, there are genes responsible for the synthesis of IgE. There are many studies of the C-159T polymorphism (rs2569190) of the *CD14* receptor gene in atopic patients [4]. For this polymorphism, cytosine (C) is replaced by thymine (T) at position 159 of the promoter region, resulting in the population presence of homozygotes of cytosine and thymine (CC, TT) and heterozygotes cytosine-thymine (CT) [3].

This polymorphism can affect the development of various diseases in different ways. The risk of nasal allergies and atopy was the most reduced in the subjects who combined both an early-life exposure to a farming environment and the -159TT genotype [5]. Although children with C/C variant of *CD14* C-159T had a significantly lower prevalence of croup [6].

It has been shown that the number of positive skin tests was significantly higher in patients with CC genotype compared with TT [3]. In the Netherlands, it was found that in patients with positive skin tests, the level of total IgE was significantly ($p < 0.05$) higher in CC compared to TT genotype [7]. In Australia, it was found that the risk of atopy in children is significantly higher in CC genotype (OR = 2.0, $P = 0.04$) [8]. In China, one study has shown that atopic subjects with CC genotype had the highest serum total IgE levels compared with CT and TT genotypes [9]. Another research has shown that TT homozygotes are more common in adult patients with allergic rhinitis among the Chinese population and the C-159T polymorphism was not associated with serum IgE levels [10]. Other studies indicate that C-159T gene polymorphism can be associated with elevated levels of soluble CD14 [11], [12].

In turn, probiotics have antagonistic properties regarding activation mechanisms of inflammation, including endotoxin-dependent ones. So, probiotics stimulate regulatory T-lymphocytes, increase the synthesis of IF- β and TGF- β , inhibit the function of T-helper type 2, reduce the secretion of TNF- α and eosinophilic cationic protein, reduce the concentration of total and specific IgE, reduce colonisation of the skin by *Staphylococcus aureus* and restore its barrier function [13].

Identifying phenotypes and genotypes, on the one hand, and potential biomarkers on the other, are vital elements for the successful development of new and personalised therapeutic approaches in patients with AD [14].

The purpose of the study was to investigate the efficacy of adding probiotic (*Lactobacillus acidophilus*, LA-5 and *Bifidobacterium animalis* subsp. *lactis*, BB-12) to standard treatment (ointment of fluticasone propionate 0.005% and emollient) of atopic dermatitis in adults during 28 days, depending on the stratification of patients on CC or TT genotypes of the *CD14* receptor gene.

Material and Methods

The study included 37 adult patients with AD. For the diagnosis of atopic dermatitis, we used the recommendations provided by the European Academy of Dermatology and Venereology [15].

All patients with atopic dermatitis, depending on the level of total IgE and at least one allergen's positivity by skin prick tests, were divided into two main groups: exogenous or IgE-dependent AD (total IgE level greater than 100 IU/ml) and endogenous IgE-independent AD (total IgE level less than 100 IU/ml). The level of total IgE was determined by ELISA method.

There were identified 19 patients with exogenous (IgE-dependent) and 18 with endogenous (IgE-independent) AD.

Allele-specific PCR with electrophoretic detection was used to access gene polymorphisms of the *CD14* receptor (C-159T, rs2569190). Allele-specific PCR was performed using kit: "Mutation of monocyte differentiation antigen (CD14) C-159T" (Lytech, Russia) according to the manufacturer's instructions.

The level of IL-4, IL-5, IL-10, TGF- β in serum was determined by ELISA method.

Determination of the severity of the disease was carried out using SCORAD (SCORing Atopic Dermatitis) index [16]. The quality of life of the patients was assessed using the DLQI questionnaire (Dermatitis Quality of Life Index) [17].

The clinical trial was conducted as open, controlled, randomised, in 6 parallel groups during 28 days at the departments of dermatology and clinical, laboratory immunology and Allergology of the Shupyk National Medical Academy of Postgraduate Education.

To study the efficacy of the probiotics (*Lactobacillus acidophilus*, LA-5 and *Bifidobacterium animalis* subsp. *lactis*, BB-12) on the severity of the disease, quality of life and immune parameters, genotypes of CC and TT, all patients were divided into three groups for both exogenous and endogenous AD. The first groups were selected from patients with CC genotype (C-159T) who received standard therapy (ointment of fluticasone propionate 0.005% – 2 times a day, emollients – 2 times a day) and probiotic (*Lactobacillus acidophilus*, LA-5 and *Bifidobacterium animalis* subsp. *lactis*, BB-12 - 1 capsule 2 times per day) The second group included patients with CC genotype, who received only standard therapy. The third group was presented by patients with TT genotype (C-159T) who received standard therapy and probiotic. The SCORAD and DLQI parameters were evaluated on Day 0, 14 and Day 28. The level of IL-4, IL-5, IL-10, TGF- β cytokines was determined on

Day 0 and Day 28.

All results were analysed using "Minitab 16" statistical software. In the analyses, the normality test was done using the Kolmogorov-Smirnov test. The comparison of central tendencies of two independent samples was performed using the U-Mann-Whitney test. Comparison of the average of two independent samples used Student's criterion for non-normally and normally distributed samples, respectively. Quantitative variables are presented as mean values and standard deviation (SD) or 95% confidence intervals for normally distributed data, and the median with first (Q1) and third (Q3) quartile or 95% confidence intervals for non-normally distributed data. For multiple comparisons, the Kruskal-Wallis test and ANOVA (Bonferroni and Sheffe correction) were used.

All study subjects provided written informed consent to participate in this research. Ethics approval was received from the Bioethics Committee of the Shupyk National Medical Academy of Postgraduate Education, Kyiv, Ukraine.

Results

The average age of patients with exogenous AD (28.32 ± 11.70 years) did not significantly differ ($p = 0.520$) from endogenous (29.11 ± 9.99 years) one. Groups did not differ significantly ($P = 0.851$) by gender (exogenous AD, male to male ratio 11/8; endogenous AD, female/male ratio – 10/8). The duration of the disease (exogenous AD – 17.68 ± 6.39 years, endogenous AD – 16.44 ± 7.04 , $p = 0.676$) and the number of exacerbations in the last year (exogenous AD – 3.00 ± 0.94 , endogenous AD – 2.78 ± 1.06 , $p = 0.625$) also did not significantly differ.

The assessment of the SCORAD index on Day 0, 14 and 28 are provided in Table 1.

Table 1: The dynamics of SCORAD scores in patients that underwent the different treatments

Groups	Day 0	Day 14	Day 28	P1	
Exogenous AD	CC genotype, standard therapy + probiotics, n = 7	12.00 (10.50-21.52)	6.00 (2.50-10.02)#	3.00 (2.00-5.51)#	0.001
	CC genotype, standard therapy, n = 6	12.50 (8.19-18.61)	7.50 (6.19-16.61)	5.50 (4.19-14.81)*	0.121
	TT genotype, standard therapy + probiotics, n = 6	14.00 (10.19-22.42)	8.50 (6.39-14.81)	6.50 (4.19-11.23)* #	0.015
	P2	0.786	0.132	0.022	
Endogenous AD	CC genotype, standard therapy + probiotics, n = 6	14.50 (9.19-21.42)	9.00 (6.27-12.73)#	6.00 (4.19-7.81)#	0.006
	CC genotype, standard therapy, n = 6	14.00 (11.19-20.61)	11.00 (8.39-16.03)	9.50 (7.19-13.42)*#	0.039
	TT genotype, standard therapy + probiotics, n = 6	16.00 (10.00-23.42)	11.00 (7.39-13.61)	8.50 (6.19-9.81)*#	0.011
	P2	0.891	0.558	0.020	

Note: P1 – reliability in multiple comparison with the use of the Kruskal-Wallis test in the group on Day 0, 14 and 28; P2 – reliability in multiple comparisons by using the Kruskal-Wallis test between groups; * – significance of differences between the group with the CC genotype (standard therapy + probiotics) from the groups with the CC genotype (standard therapy) and TT genotype (standard therapy + probiotics), $p < 0.05$; # – significance of differences between groups on Day 0 compared with 14 and 28, $p < 0.05$; Me – median, 95% CI – 95% confidence interval of the median.

There was estimated that standard treatment

with probiotics during 28 days significantly reduced the SCORAD index in exogenous AD patients with CC and TT genotypes (Table 1). Patients with CC genotype who received standard therapy with probiotics had the most significant reduction of SCORAD index on Day 28.

Table 2: The dynamics of DLQI scores in patients that underwent the different treatments

Groups	Day 0	Day 14	Day 28	P1	
Exogenous AD	CC genotype, standard therapy + probiotics, n = 7	10.00 (7.50-15.53)	7.00 (4.50-10.01)#	3.00 (2.00-3.50)#	0.001
	CC genotype, standard therapy, n = 6	9.50 (7.19-19.06)	6.50 (5.19-15.25)	4.50 (3.19-12.45)*#	0.037
	TT genotype, standard therapy + probiotics, n = 6	12.50 (6.19-21.42)	9.50 (4.19-14.81)	6.00 (3.19-11.61)*	0.150
	P2	0.841	0.715	0.012	
Endogenous AD	CC genotype, standard therapy + probiotics, n = 6	12.50 (6.39-19.42)	8.50 (5.00-13.42)	5.50 (3.19-8.42)#	0.034
	CC genotype, standard therapy, n = 6	11.00 (7.39-17.42)	7.00 (4.19-11.81)	4.50 (3.19-8.81)#	0.027
	TT genotype, standard therapy + probiotics, n = 6	13.50 (8.19-19.42)	10.00 (6.19-13.81)	6.00 (4.19-9.81)#	0.031
	P2	0.816	0.442	0.544	

Note: same as in Table 1.

There was a significant decrease in SCORAD index (Table 1) in patients of all groups who had endogenous AD. It was significantly lower ($p = 0.020$) in patients with the CC genotype who received standard treatment with probiotics compared to other groups.

The next step was to analyse the quality of life of patients during treatment. The assessment of the DLQI index is provided in Table 1.

Table 3: The serum level of IL-4 (pg/ml) in patients that underwent different treatments

Groups	Day 0	Day 28	P1	
Exogenous AD	CC genotype, standard therapy + probiotics, n = 7	41.70 (19.98-43.81)*	12.90 (11.50-18.43)	0.004
	CC genotype, standard therapy, n = 6	30.20 (24.34-42.51)*	24.15 (14.16-34.77)*	0.240
	TT genotype, standard therapy + probiotics, n = 6	9.80 (8.12-24.58)	9.85 (6.73-19.47)	0.699
	P2	0.014	0.010	
Endogenous AD	CC genotype, standard therapy + probiotics, n = 6	29.05 (18.87-42.11)*	23.00 (16.32-30.39)*	0.240
	CC genotype, standard therapy, n = 6	29.90 (25.13-39.56)*	24.20 (18.07-34.08)*	0.078
	TT genotype, standard therapy + probiotics, n = 6	16.35 (9.91-24.43)	12.90 (8.53-19.42)	0.310
	P2	0.017	0.023	

Note: P1 – comparison of central tendencies between 0 and day 28 using the Mann-Whitney U-test; P2 – reliability in multiple comparisons using the Kruskal-Wallis test between groups; * – significance of differences between groups with TT genotype (standard therapy + probiotics) from groups with CC genotype (standard therapy) and CC genotype (standard therapy + probiotics), $p < 0.05$; # – significance of differences between the group with CC genotype (standard therapy + probiotics) from the group with the genotype CC (standard therapy), $P < 0.05$.

For the exogenous form of AD (Table 2), there was a significant decrease in DLQI scores on Day 28 for patients in both treatment groups who had CC genotype. For patients with TT genotype, results did not reach the level of statistical significance ($p = 0.150$). On the contrary, for endogenous AD there was a significant decrease in DLQI score for all groups.

The lowest score was observed in patients with CC genotype (standard treatment + probiotics), which significantly differed ($p = 0.012$) from other groups in the exogenous form of AD.

Dynamics of the concentration of IL-4 is provided in Table 3.

On Day 0, the serum level of IL-4 (Table 3) in patients with TT genotype was significantly lower compared to CC genotype in both groups for exogenous and endogenous AD. On Day 28 (Table 3), there was a significant decreased ($p = 0.004$) of this cytokine only in patients with CC genotype and exogenous form of AD who received standard therapy with probiotics. For endogenous AD, no such significant changes have been observed.

Table 4: The serum level of IL-5 (pg/ml) in patients that underwent different treatments

Groups		Day 0	Day 28	P1
Exogenous AD	CC genotype, standard therapy + probiotics, n = 7	30.70 (23.18-43.16)*	23.10 (16.74-35.14)*	0.074
	CC genotype, standard therapy, n = 6	28.80 (20.68-44.06)*	24.50 (15.72-34.93)*	0.132
	TT genotype, standard therapy + probiotics, n = 6	20.50 (10.64-25.46)	13.85 (9.62-21.56)	0.240
	P2	0.023	0.048	
Endogenous AD	CC genotype, standard therapy + probiotics, n = 6	28.10 (20.59-45.97)*	24.65 (15.64-37.95)*	0.394
	CC genotype, standard therapy, n = 6	35.40 (29.87-48.62)*	29.85 (24.59-39.20)*	0.240
	TT genotype, standard therapy + probiotics, n = 6	15.80 (9.77-23.45)	12.40 (8.86-18.91)	0.379
	P2	0.003	0.004	

Note: same as in Table 3.

In patients with TT genotype, the level of IL-5 (Table 4) was significantly lower in comparison to other groups on Day 0 and on Day 28. During treatment, the concentration of IL-5 (Table 4) did not significantly change in any of the studied groups.

Table 5: The serum level of IL-10 (pg/ml) in patients that underwent different treatments

Groups		Day 0	Day 28	P1
Exogenous AD	CC genotype, standard therapy + probiotics, n = 7	15.40 (10.15-26.45)*	22.20 (13.65-30.20)*	0.210
	CC genotype, standard therapy, n = 6	19.25 (11.98-26.52)*	18.90 (14.69-32.67)*	0.589
	TT genotype, standard therapy + probiotics, n = 6	44.65 (39.99-56.23)	46.75 (37.01-62.68)	0.818
	P2	0.003	0.003	
Endogenous AD	CC genotype, standard therapy + probiotics, n = 6	25.70 (16.34-37.96)*	27.70 (19.87-38.24)*	0.749
	CC genotype, standard therapy, n = 6	23.55 (16.68-43.63)*	25.20 (21.07-46.01)*	0.589
	TT genotype, standard therapy + probiotics, n = 6	58.45 (37.61-70.55)	67.85 (47.97-75.34)	0.485
	P2	0.008	0.004	

Note: same as in Table 3.

In turn, the concentration of IL-10 (Table 5) was significantly higher at the beginning and the end of treatment in the groups of patients with TT genotype compared to CC genotype. The treatment of exogenous and endogenous AD did not lead to significant changes in the level of IL-10.

Table 6: The serum level of TGF- β (pg/ml) in patients that underwent different treatments

Groups		Day 0	Day 28	P1
Exogenous AD	CC genotype, standard therapy + probiotics, n = 7	16.10 (13.69-21.61)*	35.90 (28.64-47.48)#	0.001
	CC genotype, standard therapy, n = 6	17.40 (12.91-25.43)*	18.30 (13.84-20.10)*#	0.998
	TT genotype, standard therapy + probiotics, n = 6	41.90 (31.81-50.34)	39.85 (32.66-52.83)	0.998
	P2	0.003	0.002	
Endogenous AD	CC genotype, standard therapy + probiotics, n = 6	16.70 (11.12-32.59)*	18.20 (12.84-29.77)*	0.818
	CC genotype, standard therapy, n = 6	17.75 (13.17-26.64)*	17.95 (12.12-29.88)*	0.810
	TT genotype, standard therapy + probiotic, n = 6	46.90 (34.86-50.23)	46.85 (37.12-53.04)	0.631
	P2	0.003	0.003	

Note: same as in Table 3.

The dynamics of TGF- β in contrast to IL-10 was different. Thus, in patients with CC genotype and exogenous form of AD (Table 6) who received standard treatment and probiotics, the level of TGF- β ($p = 0.001$) was significantly increased by Day 28 compared to Day 0. Also, the level of TGF- β in this group on Day 28 did not significantly differ from the group with TT genotype. In all other cases, the concentration of this cytokine in TT genotype (Table 6) was significantly higher compared to CC genotype.

Discussion

A possible explanation is that there is a high activity of type 2 immune response in patients with an exogenous form of AD with CC genotype. Probiotics are likely to cause the most active suppression of inflammation precisely in such a cohort of patients.

A randomised double-blinded placebo-controlled pilot study showed significantly improved oxidative stress values during probiotics treatment in inflammatory bowel disease [18]. In another clinical trial, it was shown that probiotics supplementation reduced the incidence of infections in the oral cavity and respiratory tracts without any drugs-related adverse effects [19].

It has been investigated that the positive effect of probiotics comes from several possible immunological mechanisms, including the modulation of T_H cell activation, the induction of regulatory T-lymphocytes (Treg), and improved restoration of the barrier function [20]. Probiotic bacterial strains have been shown to inhibit T_H-2 cell responses and stimulate the production of cytokines by T-helper type 1 [21]. Also, the use of probiotics increases the number of populations of T-regulatory lymphocytes in experimental models of allergic diseases, including AD [22], [23], most likely inducing regulatory dendritic cells [24].

In a randomised, double-blind, placebo-controlled study, clinical efficacy in the administration of probiotic strains (*Lactobacillus salivarius* LS01) in the treatment of adult AD patients was evaluated. There were included 38 AD patients who took probiotics for 16 weeks. Patients receiving probiotics showed a statistically lower SCORAD ($p < 0.0001$) and DLQI ($p = 0.021$) indices at the end of treatment compared to the placebo group. It has also been shown that the treatment of *L.salivarius* LSO1 reduces the production of cytokines Th2 type while maintaining a stable concentration of Th1 cytokines. At the end of treatment, there was also a statistically significant decrease in staphylococci in faeces in patients taking probiotics [25].

In this pilot study we found that the addition of probiotics (*Lactobacillus acidophilus*, LA-5 and *Bifidobacterium animalis* subsp. *lactis*, BB-12) to standard treatment protocol of AD (ointment of fluticasone propionate 0.005%, emollient) significantly increased the effectiveness of treatment of atopic dermatitis in adults with exogenous form and CC genotype (C-159T). Favourable outcome was confirmed by clinical (a significant decrease of SCORAD and DLQI indices) and immunological criteria (a significant decrease of IL-4 and an increase of TGF- β).

Interpretation of the results of this study is based on data of a small number of patients, which requires further study of this problem with the involvement of more patients.

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