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METHOTREXATE EFFECT ON BIOCHEMICAL INDICES OF PSORIASIS PATIENTS DEPENDS ON *MTHFR* GENE POLYMORPHISM

O. M. FEDOTA[1], L. V. ROSCHENYUK[2,3], T. V. TYZHNENKO[1], N. G. PUZIK[1,3], V. M. VORONTSOV[1], P. P. RYZHKO[1]

[1]V.N. Karazin Kharkiv National University, Ukraine;
[2]Kharkiv Regional Clinical Skin and Venereal Diseases Dispensary №1, Ukraine;
[3]Kharkiv National Medical University, Ukraine;
e-mail: tyzhnenko@ukr.net

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Methotrexate (MTX) is the immunosuppressive anti-inflammatory drug and the antagonist of the enzyme dihydrofolate reductase. Pharmacogenomic studies and clinical evidences suggest that altered response to MTX in patients with different diseases is associated with polymorphisms of genes that regulate folate metabolism. The purpose of the article was to analyze the methotrexate effect on the biochemical indices of psoriasis patients depending on methylenetetrahydrofolate reductase gene (MTHFR) polymorphisms. Effects of two single-nucleotide polymorphisms, C677T and A1298C, were studied. An increase of alanine aminotransferase and aspartate aminotransferase activity above the normal level in the patients with both MTHFR gene polymorphisms after methotrexate intake was observed. In patients with CC, TT, CT genotypes for C677T polymorphism and AA genotype for A1298C polymorphism of MTHFR gene, significant differences in alpha-amylase activity before and after treatment with methotrexate were detected. Analysis of the biochemical indices of patients with arthropathic and vulgaris psoriasis showed that the positive effect of MTX treatment could be associated with wild-type alleles in both polymorphisms of MTHFR gene, while the ineffectiveness of methotrexate was associated with the diheterozygous genotype. The largest number of smokers was found within the CTAA genotype group (37.5%), while no smokers were observed within TTAA patients and most of CCAA patients. The data obtained testify the utility of the individual approach to the psoriasis patients therapy taking into account genetic background.

K e y w o r d s: psoriasis, folate cycle, MTHFR gene, C677T, A1298C, single-nucleotide polymorphism (SNP), methotrexate, smoking.

Individualization of pharmacotherapy based on the patients' genetic background allows to increase the effectiveness of treatment and reduce costs [1, 2]. Psoriasis is a heterogeneous chronic painful, disfiguring disease. Joints deformations and disability are the most prominent extracutaneous manifestations of this condition [3]. Currently, psoriasis is considered as a systemic disease affecting multiple organs. Cardiovascular, neurological and mental disorders could be observed in psoriasis patients [4]. The use of drugs of different pharmacological groups could be accompanied by a various response of patients to therapy, including serious complications depending on the symptoms, organ function, gender, age, diet, genotype, and others [5, 6].

Methylenetetrahydrofolate reductase (MTHFR) is one of the main regulatory enzymes in the folate and homocysteine metabolic pathways. Polymorphisms of *MTHFR* (OMIM 607093) gene lead to decreased activity of enzyme, lower efficiency of the homocysteine-methionine cycle and hyperhomocysteinemia. *MTHFR* gene polymorphisms effects are not only detected in patients with cardiovascular, nervous, mental, dermatological, reproductive, oncological, chromosomal and other

diseases but are also shown to depend on smoking, coffee and alcohol consumption, diet features, physical activity [7, 8].

Therefore, multifactorial pathology could be considered in terms of psoriasis, reflecting the interaction between genetic and environmental factors.

One of the main objectives of psoriasis pharmacotherapy is to find treatment options that quickly and firmly suppress and prevent further progression of the disease. Methotrexate (MTX) is the drug with anti-inflammatory and immunosuppressive action and an antagonist of the enzyme dihydrofolate reductase, that blocks the synthesis of tetrahydrofolate and therefore prevents the synthesis of purines and pyrimidines [9, 10]. Pharmacogenomic studies and clinical evidences suggest that altered response to MTX in patients with different diseases is associated with polymorphisms of folate metabolism genes [11].

Methylenetetrahydrofolate reductase is known as an enzyme that mediates MTX pharmacokinetics [12]. The interconnection between *MTHFR* gene polymorphisms (OMIM 607093) responses to MTX treatment and adverse reactions to MTX was discovered in patients with rheumatoid arthritis [13]. MTX was effective without any adverse effects in psoriasis patients with positive presumed 677C-1298A SNP haplotypes. At the same time no association between SNPs in *FPGS*, *GGH* and *MTHFR* genes and either MTX efficacy or toxicity in patients with psoriasis in the UK were shown. The assumption about the high risk of adverse effects development after MTX administration in carriers of the 677T allele of the *MTHFR* gene was not confirmed in patients with psoriasis arthritis [14]. According to the results of researches in Algeria, association between the 677T allele, methotrexate-induced toxicity and adverse effects was detected, while the C allele, in contrast, had a protective effect against MTX toxicity in patients with rheumatoid arthritis. A response to the treatment (good or moderate) was observed more often in A1298 allele carriers than in carriers of 1298C allele associated with a reduced response [15]. Generally, research results evaluating the role of individual SNPs in response to MTX were ambiguous. This could be attributed to different study designs, insufficient statistical power and folate supplementation, MTX dose, duration and route of administration and concurrent therapies [15]. Moreover, it is known that alleles and genotypes frequencies distribution, of folate metabolism genes showed ethnic and geographical patterns, so studies of one-carbon metabolism genes are actually carried out in each population. Pharmacogenetic studies on methotrexate therapy in the Ukrainian population enable the development of an effective and targeted therapeutic strategy.

The purpose of the article was to analyze methotrexate effect on the biochemical parameters of psoriasis patients depending on methylenetetrahydrofolate reductase gene (*MTHFR*) polymorphisms and to evaluate the response to therapy.

Materials and Methods

The study included a retrospective analysis of the medical history of 41 patients with psoriasis. Patients age ranged from 19 to 77 years, mean age was 46.27±1.78 years. All participants had signed the informed consent before the study. Screening included standardized questionnaires for personal data and clinical measurements such as age, sex, medical and family history of psoriasis. The liver function tests were carried out in all patients at the beginning and at the end of methotrexate treatment. Genotyping of patients according to the C677T and A1298C polymorphisms was carried out by PCR-RFLP and allele-specific PCR [16, 17]. The data were accumulated on clinical observations of adverse and favorable reactions in patients with psoriasis who were on methotrexate treatment [18]. The data distribution was tested for normality before further statistical analyses by the Kolmogorov-Smirnov and Shapiro-Wilk tests. Wilcoxon test was used for determination of difference between the means of two groups before and after methotrexate treatment. Kruskal-Wallis test value was calculated in order to establish significant differences between continuous dependent variable by a categorical independent variable. Biochemical parameters were presented as mean ± standard error of mean (M±SEM). All statistical tests were two-tailed and a probability (P) value of 5% or less was considered statistically significant.

Results and Discussion

We evaluated the relation of *MTHFR* gene polymorphisms with the main biochemical metabolic parameters before/after taking methotrexate.

Stratification of psoriatic patients by genotype according to C677T of *MTHFR* gene showed the prevalence of heterozygotes CT (25 persons) and homozygotes CC (12 persons) compared to TT homozygotes (4 persons). A similar situation was observed when considered genotypes of A1298C polymorphism in *MTHFR* gene, where the prevalence

of AA homozygotes and heterozygotes AC was observed in comparison with the CC homozygotes (29, 10 and 0 patients, respectively). The most prevalent genotype of C677T was CT in the groups of patients with vulgaris psoriasis (83.33%) and arthropathic psoriasis (51.72%). The most prevalent genotype of A1298C SNP was AA in the group of patients with arthropathic psoriasis (85.19%), while in vulgaris psoriasis patients group the frequencies of homo- and heterozygotes of A1298C SNP in *MTHFR* gene were equal.

Among arthropathic psoriasis patients with SNP C677T, those with CT genotype had the lowest alanine aminotransferase (ALT) activity compared to CC and TT genotypes. The level of activity before and after methotrexate treatment by patients with CT genotype was within the normal range, as opposed to persons with CC and TT genotypes. The same trend was noted for aspartate aminotransferase (AST) activity (Table 1). A significant change in the parameters of α-amylase activity and urea level was noted for all three genotypes, and there were differences between the genotypes. The deviations from the normal range were noted for creatinine in TT genotype, total protein in CC genotype, and total cholesterol in CT genotype (Table 1).

Psoriasis vulgaris patients with CC genotype had reduced levels of α-amylase activity (19.74±8.58)

Table 1. Biochemical characteristics of arthropathic psoriasis patients depending on C667T of MTHFR genotypes before and after methotrexate therapy

Parameter (normal range)	Before/After MTX treatment	CC, N = 10	CT, N = 15	TT, N = 4	*P* (Kruskal-Wallis test)
ALT, (0.10–0.68 mmol/lh)	Before	0.62 ± 0.08	0.57 ± 0.05	0.98 ± 0.25*	**0.032805**
	After	0.77 ± 0.08	0.69 ± 0.09	1.42 ± 0.06*	**0.000654**
	P (Wilcoxon test)	0.202623	**0.026757**	0.144128	–
AST, (0.10–0.45 mmol/lh)	Before	0.40 ± 0.05	0.35±0.03	0.53 ± 0.09	0.134523
	After	0.45 ± 0.07	0.41 ± 0.06	0.72 ± 0.04	0.035220
	P (Wilcoxon test)	0.386271	0.255989	0.144128	–
Bilirubin, (2–17 μmol/l)	Before	16.86 ± 0.84	16.56 ± 0.47	16.97 ± 0.81	0.912228
	After	17.23 ± 0.85	17.15 ± 0.36	18.36 ± 0.38	0.523244
	P (Wilcoxon test)	0.444587	0.232980	0.067890	–
α-Amylase, (25–125 IU/l)	Before	29.59 ± 3.08	29.81 ± 3.53	27.81 ± 1.13	0.953281
	After	21.20 ± 2.98	23.07 ± 1.88	30.70 ± 0.25	0.129310
	P (Wilcoxon test)	**0.036659**	**0.010594**	**0.067890**	–
Urea, (1.70-8.30 mmol/l)	Before	4.85 ± 0.31	4.59 ± 0.25	5.60 ± 0.36	0.182647
	After	5.65 ± 0.32	5.37 ± 0.25	6.43 ± 0.13	0.148415
	P (Wilcoxon test)	**0.021825**	**0.008985**	**0.067890**	–
Creatinine, (44–115 μmol/l)	Before	48.45 ± 10.67	50.07 ± 8.12	33.26 ± 19.16	0.662706
	After	62.12 ± 7.22	63.22 ± 4.72	68.95 ± 0.89	0.826595
	P (Wilcoxon test)	0.284504	0.111770	**0.067890**	–
Total protein, (65.0–85.0 g/l)	Before	80.24 ± 2.13	76.89 ± 0.96	78.63 ± 1.34	0.259128
	After	76.58 ± 1.37	77.63 ± 0.85	79.43 ± 1.52	0.428144
	P (Wilcoxon test)	**0.036659**	0.649563	1.000000	–
Total cholesterol, (3–6.26 mmol/l)	Before	5.20 ± 0.26	5.16 ± 0.09	6.14 ± 0.41*	**0.027209**
	After	5.19 ± 0.29	5.75 ± 0.28	6.61 ± 0.07	**0.055638**
	P (Wilcoxon test)	0.798860	**0.060894**	0.273323*	–

Note: *significant difference revealed with Kruskal-Wallis test in the biochemical parameters in TT group compared to CC and CT groups with C667T polymorphism of *MTHFR* gene.

and creatinine level (33.39±33.31), whereas patients with CT genotype had increased bilirubin level (17.40±0.64). After taking methotrexate, patients with both genotypes showed an increase in the ALT and AST activity above the normal limit: ALT – 0.93±0.25 (CC), 0.81±0.12, AST – 0.49±0.20 (CC), 0.51±0.09 (CT).

Positive effect of C677T and A1298C in *MTHFR* genotypes on the biochemical parameters of arthropathic psoriasis patients followed the pattern CTAC > CTAA > CCAC > CCAA > TTAA (Table 3). A similar trend was observed for the biochemical parameters in psoriasis vulgaris patients, genotyped by two SNPs in *MTHFR* gene: CTAC > CCAC > CTAA > CCAA (Table 4). Our results correspond to the data obtained by other authors, who studied the reaction of patients with rheumatoid arthritis on MTX - T allele was associated with nonresponsiveness to the drug [19]. According to the literature data, the response of psoriasis patients to drug therapy could be determined by *MTHFR* polymorphisms, with *MTHFR* 677CC serving as a predictor of high drug sensitivity, and the *MTHFR* 677 (CT, TT) and *MTHFR* 677T-1298A haplotypes serving as possible predictors of MTX adverse effects [13].

Considering the dynamics of transaminases activity, the protective effect of several SNPs in *MTHFR* gene against liver toxicity was assumed in psoriasis patients. In the studies the increased ALT and AST activity by more than 1.5 times was considered as significant hallmark of hepatotoxicity. Along with structural and functional liver damage, the serious complication of methotrexate treatment is nephrotoxicity [20], that could be noted by the dynamics of creatinine levels for some genotypes in our research (Table 1-4).

In the presented study, α-amylase activity in psoriasis patients after methotrexate treatment in most cases was within the normal range or lower. Kidney function is a crucial modifier that affects the clearance of circulating amylase in the blood [21]. Certain pharmacotherapeutics were reported to increase serum amylase level [22]. It is known that T allele leads to a decreased rate of 5.10-MTHF conversion to 5-MTHF, which results in a low rate of homocysteine remyelation, thereby increasing the homocysteine level and decreasing folic acid level in blood plasma [23]. It is also known that low levels of folate contribute to ALT elevation in serum [24]. It is proved that smoking increases plasma homocysteine level [25]. Therefore, polymorphisms C677T and A1298C and smoker status could affect the level of ALT and AST in serum.

Our analysis showed that among the examined group of patients, 81.3% of persons were smokers or had a long history of smoking in the past. The smoker experience ranged from four to several decades. The distribution of genotypes could be represented as CTAA (37.5%) > CTAC (25.0%) > CCAC (12.5%) > CCAA (6.25%) > TTAA (0%), the largest number of smokers were found within CTAA genotype group. TTAA patients and most of CCAA patients did not smoke. The distribution of genotypes and ALT parameters in smokers before/after taking methotrexate was: CTAA (0.63±0.06/0.83±0.10) > CTAC (0.57±0.05/0.60±0.02) > CCAC (0.53±0.02/0.65±0.03). Patients with genotypes TTAA and CCAA showed the highest rates and dynamics of ALT – 0.98±0.25/1.42±0.06 and 0.65±0.08/0.85±0.10, which was probably one of the smoking prevention factors in these persons.

The differences in the gene pool indicate both specific risks and a unique system of genetic markers for each ethnic group, which could be considered while forming risk groups and choosing a treatment strategy.

Our study demonstrated that patients with wild-type alleles of *MTHFR* gene responded well to methotrexate treatment. The study of *MTHFR* gene polymorphisms association with the biochemical parameters of response to methotrexate in patients with various forms of psoriasis showed that the decrease of therapeutic effect occurred in persons with CTAC genotype of C667T and A1298C polymorphisms of *MTHFR* gene. The genotypes distribution of the smokers was represented as CTAA (37.5%), CTAC (25.0%), CCAC (12.5%), CCAA (6.25%), TTAA (0%), the largest number of smokers were found within CTAA genotype group, while TTAA patients and most of CCAA patients did not smoke. The data obtained in our research will allow the development of pharmacotherapy in dermatology, which consists in predicting the effectiveness of therapy for psoriasis patients with methotrexate, taking into account genetic background.

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Table 2. Biochemical characteristics of psoriasis patients depending on A1298C of MTHFR genotypes before and after methotrexate therapy

Parameter (normal range)	Before/After MTX treatment	Arthropatic psoriasis			Vulgaris psoriasis		
		AA, N = 23	AC, N = 4	*P* (Kruskal-Wallis test)	AA, N = 6 (5)	AC, N = 6	*P* (Kruskal-Wallis test)
ALT, (0.10–0.68 mmol/lh)	Before	0.70 ± 0.06	0.49 ± 0.02	0.196633	0.64 ± 0.12 (6)	0.60 ± 0.07	0.708877
	After	0.89 ± 0.08	0.58 ± 0.02	0.136329	1.07 ± 0.17 (5)	0.63 ± 0.03	**0.019021***
	P (Wilcoxon test)	**0.023457**	**0.067890**	–	**0.043115**	0.753153	–
AST, (0.10–0.45 mmol/lh)	Before	0.42 ± 0.03	0.31 ± 0.05	0.185613	0.47 ± 0.12 (6)	0.36 ± 0.04	0.425681
	After	0.51 ± 0.05	0.37 ± 0.05	0.240694	0.68 ± 0.13 (5)	0.37 ± 0.03	0.026205
	P (Wilcoxon test)	**0.094363**	0.715001	–	0.138012	1.000000	–
Bilirubin, (2–17 μmol/l)	Before	16.85 ± 0.47	16.61 ± 0.44	0.840299	15.84 ± 0.59 (6)	16.37 ± 0.71	0.715244
	After	17.62 ± 0.42	16.02 ± 0.26	0.130607	17.32 ± 0.82 (5)	17.23 ± 0.77	0.937676
	P (Wilcoxon test)	**0.048046**	0.144128	–	**0.043115**	**0.043115**	–
α-Amylase, (25–125 IU/l)	Before	30.61 ± 2.53	26.52 ± 2.59	0.518451	17.88 ± 3.66 (6)	30.55 ± 4.45	0.063222*
	After	23.93 ± 1.69	26.78 ± 1.75	0.500812	16.21 ± 1.84 (5)	27.38 ± 2.03	0.003103*
	P (Wilcoxon test)	**0.011589**	1.000000	–	0.892738	0.345448	–
Urea, (1.7–8.3 mmol/l)	Before	4.77 ± 0.22	5.28 ± 0.18	0.358733	5.39 ± 0.45 (6)	5.58 ± 0.34	0.569564
	After	5.77 ± 0.20	5.08 ± 0.24	0.179695	6.13 ± 0.79 (5)	5.69 ± 0.40	0.613588
	P (Wilcoxon test)	**0.000099**	1.000000	–	0.224917	0.463072	–
Creatinine, (44-–115 μmol/l)	Before	44.70 ± 7.00	51.35 ± 17.16	0.718925	27.29 ± 17.11 (5)	68.82 ± 1.20	**0.025247***
	After	62.45 ±.4.29	67.35 ± 2.00	0.643963	65.68 ± 18.19 (5)	67.63 ± 1.66	0.908392
	P (Wilcoxon test)	**0.030815**	0.273323	–	0.043115	0.600180	–
Total protein, (65–85 g/l)	Before	79.39 ± 0.97	74.58 ± 2.56	**0.069956**	78.68 ± 2.35 (6)	78.08 ± 1.97	0.877892
	After	77.76 ± 0.79	77.65 ± 1.39	0.957849	76.38 ± 4.56 (5)	78.48 ± 1.72	0.653648
	P (Wilcoxon test)	**0.068017**	0.465209	–	0.500185	0.916512	–
Total cholesterol (3–6.26 mmol/l)	Before	5.34 ± 0.15	5.47 ± 0.17	0.724562	5.57 ± 0.26 (6)	5.54 ± 0.31	0.951776
	After	5.84 ± 0.22	5.39 ± 0.32	0.421453	5.79 ± 0.32 (5)	5.59 ± 0.21	0.604549
	P (Wilcoxon test)	**0.025385**	0.715001	–	0.500185	0.753153	–

Note: *significant difference revealed with Kruskal-Wallis test in the biochemical parameters in AA group compared to AC group with A1298C polymorphism of *MTHFR* gene.

Table 3. Biochemical characteristics of arthropathic psoriasis patients, depending on C667T and A1298C of MTHFR genotypes before and after methotrexate therapy

Parameter (normal range)	Before / After MTX treatment	CCAA, N = 8	CC-AC, N = 1	CTAA, N = 11	CTAC, N = 3	TTAA, N = 4	P (Kruskal-Wallis test)
ALT, (0.10–0.68 mmol/lh)	Before	0.67 ± 0.09	0.51	0.61 ± 0.06	0.48 ± 0.02	0.98 ± 0.25	**0.076170***
	After	0.81 ± 0.10	0.62	0.75 ± 0.11	0.57 ± 0.02	1.42 ± 0.06	**0.002458***
	P (Wilcoxon test)	0.326990	–	**0.091162**	0.108810	0.144128	–
AST, (0.10–0.45 mmol/lh)	Before	0.42 ± 0.06	0.39	0.39 ± 0.04	0.28 ± 0.07	0.53 ± 0.09	0.218441
	After	0.49 ± 0.08	0.45	0.44 ± 0.07	0.34 ± 0.06	0.72 ± 0.04	**0.083798***
	P (Wilcoxon test)	0.441209	–	0.533695	1.000000	0.144128	–
Bilirubin, (2–17 μmol/l)	Before	16.86 ± 1.06	17.21	16.80 ± 0.60	16.41 ± 0.56	16.97 ± 0.81	0.993676
	After	17.36 ± 1.06	16.01	17.54 ± 0.43	16.02 ± 0.37	18.36 ± 0.38	0.401926
	P (Wilcoxon test)	0.400815	–	0.247747	0.285050	**0.067890**	–
α-Amylase, (25–125 IU/l)	Before	31.68 ± 3.47	19.41	30.85 ± 4.78	28.89 ± 1.47	27.81 ± 1.13	0.876998
	After	22.15 ± 3.58	22.19	22.76 ± 2.13	28.31 ± 1.21	30.70 ± 0.25	0.217387
	P (Wilcoxon test)	**0.035693**	–	**0.016369**	0.592980	**0.067890**	–
Urea, (1.7–8.3 mmol/l)	Before	4.77 ± 0.38	5.50	4.47 ± 0.32	5.20 ± 0.24	5.60 ± 0.36	0.193251
	After	5.76 ± 0.36	4.43	5.53 ± 0.30	5.30 ± 0.14	6.43 ± 0.13	0.234141
	P (Wilcoxon test)	**0.017291**	–	**0.007646**	0.285050	**0.067890**	–
Creatinine, (44–115 μmol/l)	Before	51.80 ± 11.46	0.09	43.71 ± 10.50	68.43 ± 2.28	33.26 ± 19.16	0.876707
	After	60.96 ± 9.06	61.90	61.16 ± 6.40	69.17 ± 1.19	68.95 ± 0.89	0.862838
	P (Wilcoxon test)	0.674424	–	0.130666	0.592980	**0.067890**	–
Total protein, (65.0–85.0 g/l)	Before	80.99 ± 2.48	81.80	78.50 ± 0.82	72.17 ± 1.22	78.63 ± 1.34	0.100133
	After	77.48 ± 1.55	74.10	77.35 ± 1.13	78.83 ± 1.03	79.43 ± 1.52	0.782961
	P (Wilcoxon test)	**0.068704**	–	0.247747	0.108810	1.000000	–
Total cholesterol, (3–6.26 mmol/l)	Before	5.19 ± 0.32	5.74	5.16 ± 0.09	5.38 ± 0.20	6.14 ± 0.41	**0.069186***
	After	5.33 ± 0.34	4.78	5.92 ± 0.35	5.59 ± 0.35	6.61 ± 0.07	0.126416
	P (Wilcoxon test)	0.674424	–	**0.032855**	1.000000	0.273323	–

Note: *significant differences revealed with Kruskal-Wallis test in the biochemical parameters in TTAA group compared to CCAA, CTAA and CTAC groups with C667T and A1298C polymorphisms of *MTHFR* gene.

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Table 4. Biochemical characteristics of psoriasis vulgaris patients depending on C667T and A1298C of MTHFR genotypes before and after methotrexate therapy

Parameter (normal range)	Before / After MTX treatment	CCAA, N = 1	CCAC, N = 1	CTAA, N = 5 (4)	CTAC, N = 5	P (Kruskal-Wallis test)
ALT, (0.10– 0.68 mmol/lh)	Before	0.52	0.54	0.66 ± 0.14 (5)	0.61 ± 0.08	0.910531
	After	1.18	0.68	1.05 ± 0.21 (4)	0.62 ± 0.03	0.170531
	P (Wilcoxon test)	–	–	**0.067890**	0.892738	–
AST, (0.10–0.45 mmol/lh)	Before	0.33	0.40	0.49 ± 0.14 (5)	0.36 ± 0.05	0.793056
	After	0.69	0.29	0.68 ± 0.16 (4)	0.38 ± 0.03	0.215047
	P (Wilcoxon test)	–	–	0.273323	0.589639	–
Bilirubin, (2–17 μmol/l)	Before	15.54	15.20	15.90 ± 0.72 (5)	16.60 ± 0.82	0.870154
	After	16.01	17.40	17.65 ± 0.96 (4)	17.20 ± 0.94	0.907968
	P (Wilcoxon test)	–	–	**0.067890**	**0.067890**	–
α-Amylase, (25–125 IU/l)	Before	26.57	45.49	16.14 ± 3.94 (5)	27.56 ± 4.03	**0.084393***
	After	11.16	28.31	17.48 ± 1.73 (4)	27.19 ± 2.47	**0.029363***
	P (Wilcoxon test)	-	-	0.465209	0.685831	–
Urea, (1.7–8.3 mmol/l)	Before	4.43	6.42	5.58 ± 0.50 (5)	5.41 ± 0.36	0.603039
	After	6.81	5.61	5.96 ± 0.99 (4)	5.70 ± 0.49	0.922523
	P (Wilcoxon test)	-	-	0.465209	0.138012	–
Creatinine, (44–115 μmol/l)	Before	0.09	66.70	34.09 ± 20.27 (4)	69.24 ± 1.38	0.130466
	After	109.30	60.40	54.77 ± 18.79 (4)	69.08 ± 1.00	0.335440
	P (Wilcoxon test)	–	–	**0.067890**	0.892738	–
Total protein, (65–85 g/l)	Before	80.70	74.80	78.28 ± 2.84 (5)	78.74 ± 2.28	0.914165
	After	81.30	70.80	75.15 ± 5.66 (4)	80.02 ± 0.96	0.605001
	P (Wilcoxon test)	–	–	0.465209	0.685831	–
Total cholesterol, (3–6.26 mmol/l)	Before	5.39	4.11	5.60 ± 0.32 (5)	5.83 ± 0.15	0.159201
	After	5.61	5.12	5.83 ± 0.41 (4)	5.68 ± 0.24	0.818710
	P (Wilcoxon test)	–	–	0.715001	0.224917	–

Note: *significant difference revealed with Kruskal-Wallis in the biochemical parameters in CTAC group compared to CTAA group with n C667T and A1298C polymorphisms of *MTHFR* gene.

ВПЛИВ МЕТОТРЕКСАТУ НА БІОХІМІЧНІ ПОКАЗНИКИ ХВОРИХ НА ПСОРІАЗ ЗАЛЕЖНО ВІД ГЕНОТИПІВ ГЕНА *MTHFR*

О. М. Федота[1], *Л. В. Рощенюк*[2,3], *Т. В. Тижненко*[1], *Н. Г. Пузік*[1,3], *В. М. Воронцов*[1], *П. П. Рижко*[1]

[1]Харківський національний університет імені В. Н. Каразіна, Україна;
[2]Харківський обласний клінічний шкірно-венерологічний диспансер №1, Україна;
[3]Харківський національний медичний університет, Україна;
e-mail: tyzhnenko@ukr.net

Метотрексат (МТХ) є протизапальним та імуносупресивним препаратом, а також антагоністом ензиму дигідрофолатредуктази. Клінічні дані свідчать, що відмінності у відповіді пацієнтів із різними хворобами на МТХ пов'язані з поліморфними варіантами генів, що регулюють метаболізм фолату. Метою роботи був аналіз впливу метотрексату на біохімічні показники хворих на псоріаз із поліморфними варіантами гена метилентетрагідро-фолатредуктази (*MTHFR*). Досліджено ефекти двох однонуклеотидних поліморфізмів гена *MTHFR*: *C677T* і *A1298C*. Після прийому метотрексату в пацієнтів із різними генотипами за обома поліморфними варіантами гена *MTHFR* спостерігалося збільшення рівня аланінамінотрансферази та аспартатамінотрансферази вище діапазону референсних значень. У пацієнтів із генотипами CC, CT, TT та генотипом AA за поліморфними варіантами *C677T* та *A1298C* гена *MTHFR* було виявлено значні відмінності в рівнях α-амілази до та після лікування метотрексатом. Аналіз біохімічних показників хворих на артропатичний та вульгарний псоріаз показав, що позитивний вплив лікування метатраксатом пов'язаний з наявністю алелей дикого типу за обома поліморфними варіантами, а неефективність метотрексату за дослідженими поліморфізмами пов'язана з дигетерозиготним генотипом. Найбільшу кількість курців виявлено в групі з CTAA генотипом (37,5%), тоді як серед пацієнтів з TTAA та більшості хворих з CCAA генотипами курців не виявлено. Одержані дані можуть бути використані для персоналізованої терапії хворих на псоріаз із урахуванням генетичних особливостей пацієнтів.

Ключові слова: псоріаз, фолатний цикл, ген *MTHFR*, *C677T*, *A1298C*, однонуклеотидний поліморфізм (ОНП), метотрексат.

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