STUDY OF EFFICIENCY OF ROSACEA THERAPY DEPENDING ON TNF-α GENE RS1800629 POLYMORPHISM

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Abstract. The results of the study of the distribution frequency of the genotypes of the polymorphism of the rs1800629 TNF-α gene involved in the formation and clinical course of rosacea are revealed, which allows us to predict the development, course of the disease and to develop the optimal scheme for its prevention and treatment. We studied the polymorphism of the rs1800629 TNF-α gene in rosacea patients and determined the effectiveness of therapy depending on the severity and frequency distribution of genotypes.

Keywords: rosacea, pathogenesis, rs1800629 polymorphism of the TNF-α gene, treatment.

Introduction.

Rosacea (syn.: acne rosacea) is a chronic, widespread and often severe skin disease of the face, characterized by a stage course and refractoriness to the treatment (1, 2).

Among dermatological diagnoses, rosacea is diagnosed in 5% of the population. Until now, there is no common view on the etiology and pathogenesis of rosacea. The scientific literature contains numerous works devoted to the study of various links in the pathogenesis of rosacea (4, 7, 11).

Rosacea is often considered as the result of interactions of both exogenous (climatic, chemical, food irritants and microorganisms, in particular Demodex folliculorum) and endogenous (disruption of the gastrointestinal tract associated with Helicobacter pylori infection, neurological, endocrine, immune disorders, cardiovascular disease, vascular system) factors (5, 9, 10, 12, 13).

Numerous studies have established the pathogenetic role of vascular endothelial growth factor (VEGF), tumor necrosis factor alpha (TNF-α), interleukins (IL-1β, IL-4, IL-10), vitamin D receptor (VDR) in the genesis of rosacea. (6, 8, 11)

Currently, there are few works on the study of genes regulating the immune response and angiogenesis factors in patients with rosacea, their data are contradictory, and the number of studied cytokines is small (TNF-a, IL-1β, IL-4, IL-10, VEGF). As for the study of the effectiveness of rosacea therapy, depending on the frequency of distribution of genotypic variants of gene polymorphism in the scientific literature, there are isolated studies (3). Investigation of the frequency of genotypic variants of polymorphism of genes involved in the formation and clinical course of rosacea will make it possible to predict the development and course of the disease and to develop an optimal scheme for its prevention and treatment.

In connection with the above, the purpose of this study was to study the effectiveness of therapy depending on its severity and the distribution of the genotype frequencies of the rs1800629 TNF-α gene polymorphism in patients with rosacea.

Materials and methods. The object for the research was a sample of unrelated patients diagnosed with rosacea living in different regions of the republic (n = 140). The diagnosis of

rosacea was made on the basis of clinical symptoms, the course of the disease, confirmed by laboratory and instrumental research methods. The control group consisted of 145 apparently healthy unrelated individuals of Uzbek nationality, who corresponded in terms of sex and age to the examined group of patients and did not have a history of skin pathology.

For DNA isolation from peripheral blood lymphocytes, a Ribo-sorb set (AmpliSens®, Russia) was used. Testing of polymorphism of the rs1800629 TNF-α gene was carried out by standard polymerase chain reaction using CG-1-96 thermal cyclers "CorbettResearch" (Australia) and "Applied Biosystems" 2720 (USA), using a standardized set from OOO Litekh (Moscow), according to the manufacturer's instructions.

The deviation of the distributions of genotypes from the canonical Hardy – Weinberg equilibrium was estimated using the GenePop computer program available on the Internet (http://wbiomed.curtin.edu.au/genepop). The software package "OpenEpi 2009, Version 2.3" was used as a tool for statistical calculations.

When analyzing the distribution of genotype frequencies according to the Hardy-Weinberg law in the group of examined patients, a statistically significant deviation of the frequencies of the homozygous genotype from RHV ($\chi 2 = 6.6$; $P = 0.01$) was found, which is possibly related to the specifics of the main group. The deviation from RHV can be explained by the fact that the group of patients with rosacea is not a random population sample, but is selected based on the criteria for the presence of the disease. The identified deviation is possibly associated with a decrease in homozygosity, i.e. lack of homozygotes in the analyzed group due to an increase in the number of representatives with a heterozygous variant of the genotype (selective effect).

A comparative analysis of the allele and genotype frequencies of the polymorphism of the rs1800629 TNF-α gene between the group and subgroups of rosacea patients and the population group revealed statistically significant differences.

The frequencies of the alleles rs1800629G and rs1800629A in the main group of patients and the control group were 82.1% and 17.8% and 92.1 and 7.9%, respectively. At the same time, the distribution of alleles in the examined groups was significantly different; the unfavorable allele rs1800629A was significantly higher among the main group of patients ($\chi 2 = 12.6$; $P = 0.0004$; OR = 2.5; 95% CI 1.494, 4.263).

When comparing the samples of patients and the corresponding control, statistically significant differences in the distribution of frequencies of genotypes of this locus were also revealed ($P < 0.05$). In the group of patients, the frequency of the unfavorable heterozygous genotype rs1800629 * G / A of the TNF-α gene was significantly higher than in the control (35.7% versus 15.9%, $\chi 2 = 14.3$; $P < 0.05$; OR = 3, 0; 95% 1.677; 5.179). According to the calculated odds ratio, the risk of developing rosacea in carriers of this genotype is 3.0 times higher than that of carriers of the homozygous wild genotype (Fig. 1 and 2).

Thus, the results obtained in the course of this study reliably indicate the presence of an association between the carriage of the rs1800629 * G allele and the rs1800629 * G / A genotype of the TNF-α gene with the risk of rosacea.

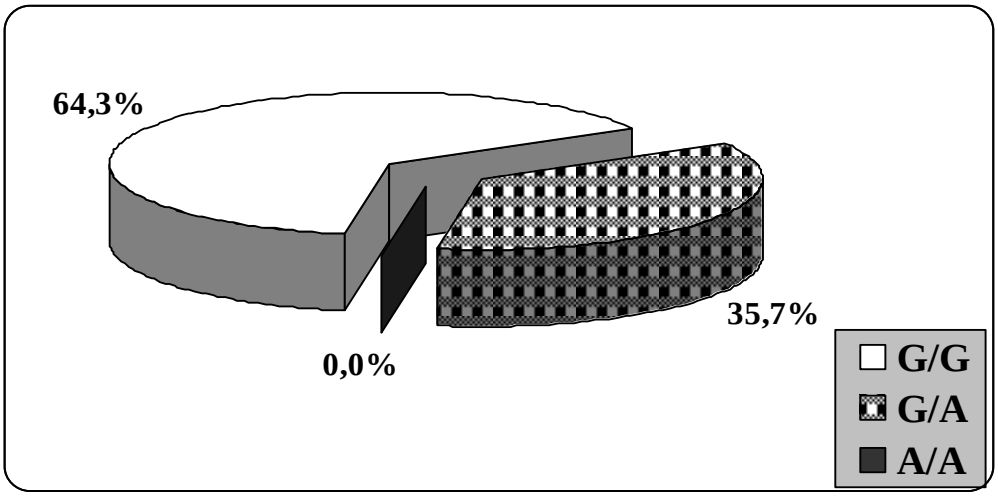

Fig. 1. Frequency of distribution of genotypes of polymorphism of the rs1800629 gene TNF-α in the main group (n = 140).

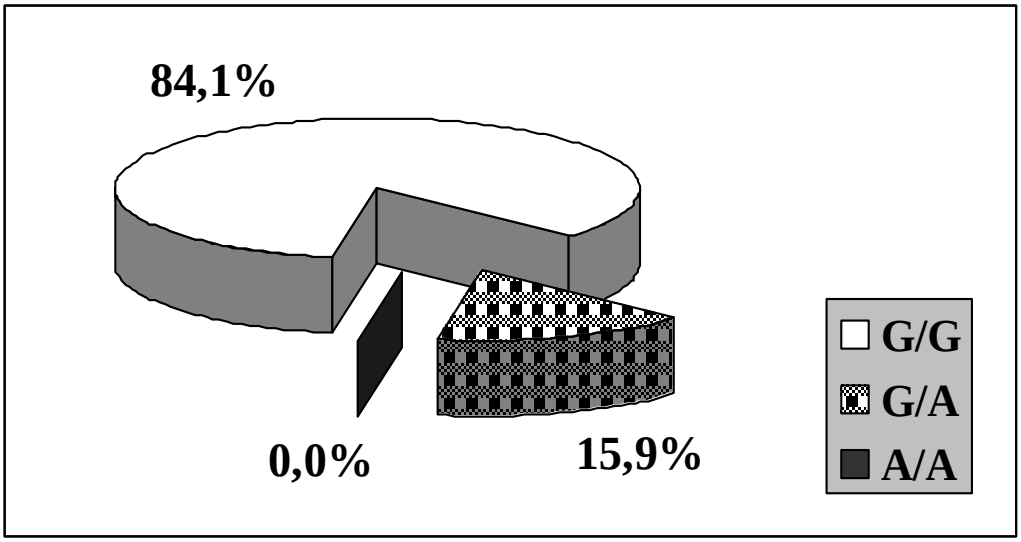

Fig.2. Frequency of distribution of genotypes of polymorphism of the rs1800629 gene TNF-α in the control group (n = 145).

All 140 patients with rosacea received therapy according to the standards of examination and treatment in dermatovenerology (2017) approved by the Ministry of Health of the Republic of Uzbekistan. Standard treatment included the following drugs: metronidazole (trichopol - 0.25 - 4 times a day for 15-20 days), antibiotics (doxycycline) - for papulopustular subtype, vitamin preparations (aevit, thiamine bromide, riboflavin mononucleotide), externally - metronidazole (0.75% cream or gel, or 1.0% cream), as well as antihistamines, sedatives (tranquilizers) drugs according to indications and external therapy was carried out depending on the pathomorphological manifestations of the disease.

The effectiveness of therapy in patients with rosacea was assessed after the course of therapy and six months after the therapy. Clinical recovery was considered in the case of complete regression of rashes and residual effects in the form of an insignificant amount of telangiectasias, significant improvement - with residual effects in the form of mild non-edematous erythema, disappearance of papule-pustules and persistence of telangiectasias and

improvement - with a slight decrease in edema and erythema, a decrease in the number of papulo-pustular elements, telangiectasias. If, after the therapy, no changes were observed in the clinical picture of the disease, then this result was regarded as the absence of a clinical effect.

As a result of therapy, without taking into account the genotype of TNF-α gene polymorphism, clinical recovery was observed in 17.9% of patients (25/140), significant improvement in 35% (49/140) and improvement in 47.1% (66/140) patients, i.e. the positive therapeutic effect in the form of clinical recovery and significant improvement was 52.9%. At the same time, in both groups of patients, the lack of effectiveness of the results or the deterioration of the skin process from the therapy was not observed.

At the next stage, we studied the effectiveness of standard therapy for rosacea, depending on the severity and frequency distribution of genotypes of TNF-α gene polymorphism.

The effectiveness of therapy in patients with rosacea with polymorphism of the rs1800629 TNF-α gene has been studied only with the wild rs1800629 * G/G and unfavorable heterozygous genotype G/A. Since in the studied groups of patients and controls, the homozygous genotype rs1800629 * A/A of the TNF-α gene was not detected.

The effectiveness of the therapy in patients with rosacea, depending on the genotypes of the polymorphism of the rs1800629 TNF-α gene, showed that out of 50 patients who were carriers of the unfavorable heterozygous genotype G/A of the polymorphism of the rs1800629 TNF-α gene, clinical recovery was observed only in 4 (8%) patients and significant recovery y - 16 (32%), i.e. a positive result in the form of clinical recovery and significant improvement was observed in 20 (40%) patients. Whereas improvement was noted in 30 (60%) patients.

In patients with the wild rs1800629 * G/G genotype of the rs1800629 TNF-α gene polymorphism, the results of the therapy were more effective than in those carriers of the G/A genotype and clinical recovery was noted in 23.3% of patients, significant improvement in 36.6% ... At the same time, in patients with the wild G/G genotype, a positive result in the form of clinical recovery and significant improvement was noted in 54 (60%) patients, versus 40% with the G/A genotype. The results of therapy for rosacea patients, depending on the rs1800629 genotypes of the TNF-α gene, are shown in Table 1.

Table 1.: Results of therapy in rosacea patients depending on rs1800629 genotypes of TNF-α gene

№	Results of therapy	G/A		G/G	
		abs.	%	abs.	%
1	Clinical recovery	4	8	21	23,3
2	Significant improvement	16	32	33	36,7
3	Improvement	30	60	36	40
	Total	50	100	90	100

Thus, the best effect of the therapy was observed in rosacea patients with the G/G genotype of the polymorphism of the rs1800629 TNF-α gene as compared with the G/A genotype. To improve treatment results for patients carrying the G/A genotype of the polymorphism of the rs1800629 TNF-α gene, it may be necessary to add additional funds to

the therapy in the form of systemic or local drugs to correct concomitant pathologies or physiotherapeutic procedures, taking into account the indications.

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