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Genetic Aspects of Methotrexate Resistance in Patients with Rheumatoid Arthritis

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ABSTRACT

Objective: *to study the relationship of the C3435T polymorphism of the MDR1 gene with the presence of resistance to methotrexate treatment in patients with rheumatoid arthritis.* ***Materials and Methods:*** *In our study, 76 patients with rheumatoid arthritis and 24 practically healthy volunteers took part. Polymorphism of the C3435T gene was determined using the polymerase chain reaction (PCR), which was carried out in a 7500 Fast Real Time PSR Systems (USA) amplifier.* ***Results:*** *According to the results of our studies, methotrexate resistance was detected in patients with SS genotype C3435T polymorphism of the MDR1 gene. In contrast, carriers of TT genotype showed high sensitivity to treatment and low disease activity.* ***Conclusions:*** *The interrelation of the C3435T polymorphism of the MDR1 gene with the presence of resistance to methotrexate treatment in patients with RA was established. Conducting genotyping of patients with rheumatoid arthritis before the appointment of methotrexate makes it possible to predict the presence of resistance to this drug.*

Despite the development of modern technologies, the tactics of treating patients with rheumatoid arthritis (RA) remains one of the most difficult problems of modern rheumatology. This is due to the fact that the effectiveness of basic antirheumatic drugs in RA reaches 60-65% of cases [5]. Consequently, the search for new treatment approaches, taking into account genetic aspects that make it possible to identify the causes of resistance to basic therapy, is currently considered one of the priorities in rheumatology. Moreover, its relevance is also due to the fact that inadequately selected treatment contributes to the progression of RA, which serves to increase the disability among the population against the background of gross dysfunction of the joints, leading to huge economic losses.

It is well known that currently the “gold standard” of RA treatment is methotrexate (MTX), whose goal is to achieve clinical remission or “low activity” in the framework of “EULAR”. However, despite the 50-year experience of its use, there is still no clear answer on the mechanism of action of MTX to key aspects of the pathogenesis of RA. According to literary sources, about 30% of patients are resistant to this drug [4, 6]. Therefore, today, special attention is paid to the polymorphism of the MDR1 gene, since it is responsible for resistance to various drugs, and its polymorphism can affect the pharmacokinetics of many cytotoxic drugs, including methotrexate [9]. Therefore, the purpose of our study was to investigate the relationship of the C3435T polymorphism of the MDR1 gene with the presence of MTX resistance in patients with RA.

Materials and methods. The study was conducted at the 3-City Clinical Hospital No. 3 in the rheumatology department of the city of Tashkent. The study was conducted in 76 patients (73 women, 3 men, 24-65 years old) with RA. The control group consisted of 24 healthy volunteers, without the burdened rheumatological history. RA was diagnosed according to the criteria of the American College of Rheumatology (ACR), and disease activity was calculated using the DAS28 calculator. All patients who participated in our study were prescribed basic therapy (methotrexate in monotherapy at a dose of 7.5-15 mg / week) and patients were monitored for 6 months.

For the genotyping of the C3435T MDR1 polymorphism of the gene, venous blood was taken in a volume of 3 ml from patients during their hospitalization in the rheumatology department and stored in EDTA tubes. Genomic DNA was extracted from blood samples using RIBO prep reagents (AmpliSens, Russia). For genotyping, a reagent kit was used to determine the C3435T polymorphism of the MDR1 gene (SINTOL, Russia). Polymorphism of the C3435T gene was determined using the polymerase chain reaction (PCR), which was carried out in a 7500 Fast Real Time PSR Systems amplifier (Applied Biosystems USA).

Statistical analysis. The results were subjected to static processing using the computer program EXCEL and STATISTICA 6.0. A comparative analysis was performed using the standard Pearson X2 test and the two-sided Fisher test, where $p < 0.05$ was considered statistically significant.

Results. In our study, 76 patients with RA and 24 healthy volunteers without rheumatological history were studied. All patients were genotyped for the polymorphism of the C3435T MDR1 gene. The results of genotyping are shown in fig.1.

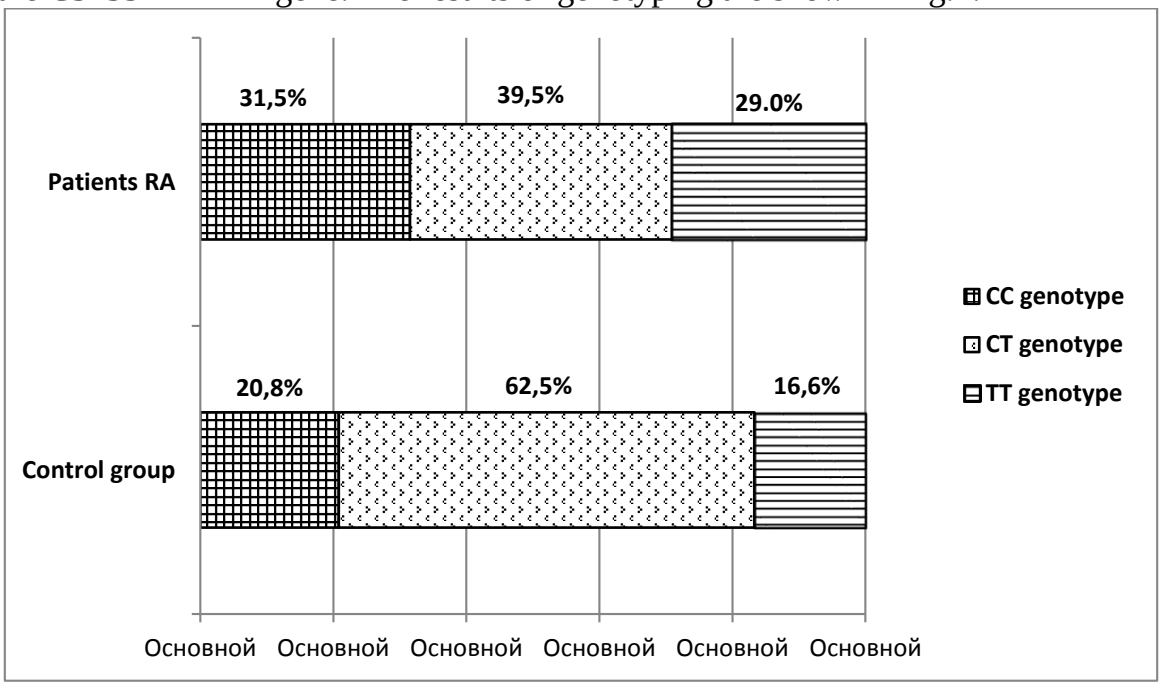

Fig.1. The percentage distribution of the genotypes of the polymorphism of the C3435T MDR1 gene in patients with RA and in the control group

As can be seen from figure 1 CC genotype of the C3435T gene was found in 31.5% of RA patients, whereas in the control group it was found in 20.8% of cases. CT genotype occurred in 39.5% of patients, and in the control group was significantly higher and amounted to 62.5% of cases. The frequency of occurrence of mutant TT genotype was 29.0% and in the control group 16.6%.

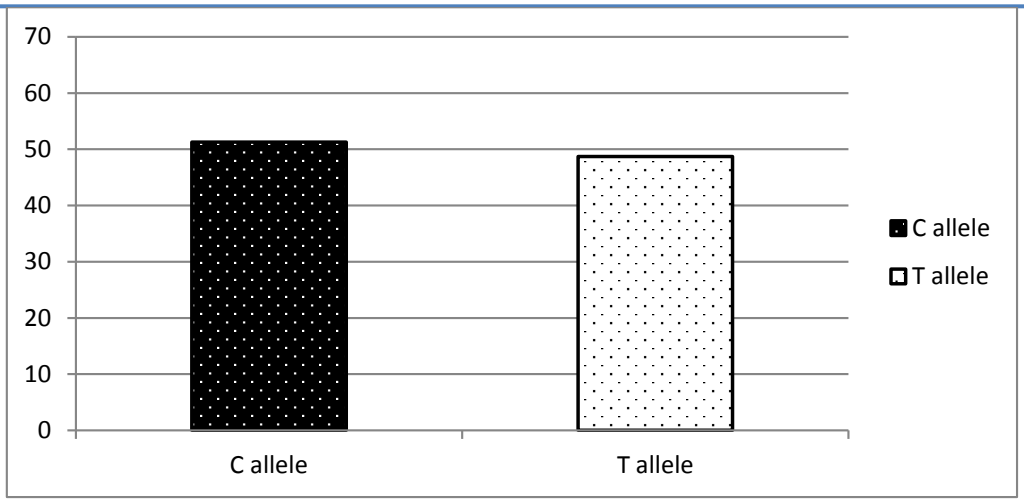

Fig.2. The distribution of the alleles of the C3435T polymorphism MDR1 gene

As can be seen from fig.2 the percentage of C and T alleles was almost the same. With the T3435C isoform allele was found in 51.3%, the T allele was found in 48.7% of RA patients.

Based on the carriage of the three genotypic variants of the C3435T polymorphism of the MDR1 gene, the following associated phenotypic groups were identified depending on the response to MTX treatment.

The "good" response to MTX (29.5%) carriers of mutant TT genotype were phenotypically characterized by a good clinical response (DAS <2.6 3-6 months) to treatment with methotrexate, as well as low disease activity.

The “poor” response to MTX (31.5%), carriers of the SS genotype were characterized by a high disease activity and a clinically poor drug response (DAS> 2.6) for treatment of MTX (Fig. 3).

The “moderate” response (39.5%) of the heterozygous CT genotype carriers showed phenotypically an average clinical response (DAS <2.6 less than 3 months) to treatment of MTX and lower disease activity compared with the “poor response” group.

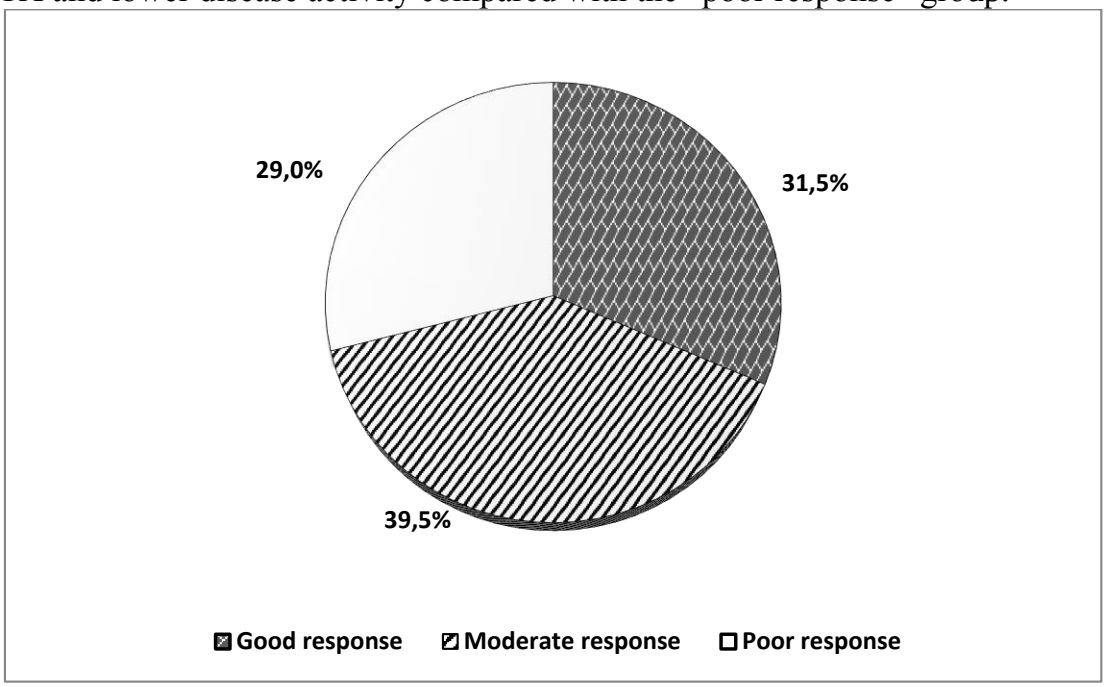

Fig. 3. Percentage distribution of RA patients depending on the drug response to treatment with methotrexate.

Discussion. As mentioned above, drug resistance is one of the important factors affecting the effectiveness of RA therapy. Individualization of pharmacotherapy, which is engaged in pharmacogenetics, consists of identifying polymorphic markers associated with a change in the body's response to drugs, developing methods for genotyping patients and introducing this approach into practical medicine. Some researchers suggest [1] that there is an association of MDR1 gene polymorphisms with the efficacy and safety of many drugs. A number of researchers (Takatori et.al., Sharma et al.) Conducted a cohort study of C3435T with the isoform of the MDR1 gene (ABCB1) in RA patients and concluded that TT genotype is associated with poor susceptibility to treatment of MTX, and CC genotype is associated with a good response to treatment. On the contrary, other researchers (Chen et.al .; Drozdzik et.al .; Pawlik et.al.) conducted the same studies and concluded that CC genotype is associated with immunity to treatment of MTX in RA.

Despite the large number of studies devoted to the study of the polymorphism of the gene MDR1, the results remain controversial, which caused us some interest. According to our data, there were no significant differences in the distribution of alleles of the C3435T polymorphism of the MDR1 gene in RA patients and conditionally healthy ones. But when comparing genotypic variants, we found differences: healthy CC and mutant TT genotypes were more common in patients, and heterozygous CT genotype was more common in healthy ones.

According to the results of genotyping, we established the relationship of the C3435T polymorphism of the MDR1 gene with the presence of resistance to MTX and disease activity. We identified three groups of respondents to treatment with this drug. Good responders - owners of the mutant TT genotype showed a good clinical response to treatment with methotrexate, as well as low disease activity (Das28 <2.6). Bad responders (patients with SS genotype) had resistance to methotrexate, even with an increase in the dose of the drug, clinical remission or low activity (Das28> 5.1) did not reach the disease. The moderate responders were CT carriers of the genotype of the C3435T polymorphism of the MDR1 gene, which showed an average drug response to MTX, and the disease activity was moderate (DAS 28 3.2–5.1).

Conclusions: Genetic studies of the C3435T polymorphism of the MDR1 gene in RA patients revealed their interrelation with resistance to MTX, as well as disease activity during treatment with this drug. Patients with RA with the CC genotype have a poor response (resistance) to treatment of MTX, as a result, the disease proceeds with a high degree of activity, compared to patients with CT and TT genotypes. Conducting genotyping of the C3435T polymorphism of the MDR1 gene in RA patients prior to administration of MTX makes it possible to predict the presence of resistance to this drug.

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