The Effect of Mdr-1 Gene Polymorphism Genotypes on The Structure and Effectiveness of Treatment of Chronic Gastritis

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Abstract

This article discusses the introduction of genotyping of patients with chronic gastritis by polymorphisms of the MDR-1 gene, especially by polymorphic marker C3435T of this gene, to ensure the effectiveness and safety of pharmacotherapy. The obtained results of pharmacoeconomics on the genotype of the C3435T polymorphism gene of the MDR1 gene in patients with chronic gastritis are also presented.

Keyword: MDR1 gene, polymorphic marker C3435T, chronic gastritis associated with H.pylori, chronic gastritis not associated with H.pylori, pharmacoepidemiology, genotyping.

Relevance

The study of genetic differences of patients for the selection of medicines (drugs) in order to increase the effectiveness of pharmacotherapy in medicine has managed to acquire paramount importance. Because the genetic characteristics of the patient serve the variability and difference of the body's response to a particular drug of pharmacotherapy [1, 18]. It should be mentioned that the genetic component is one of the main factors influencing the pharmacological response. This is also indicated by statistical data, according to which up to 60% of the variability of the body's response to the effects of drugs is associated with genetic variations of a patient with a particular disease [13]. Accordingly, the recommended introduction of the use of information about the genetic characteristics of the patient in clinical practice will allow in all areas of medicine to develop protocols for pharmacotherapy of diseases, new methods of monitoring patients, as well as reduce the risk of adverse reactions, prevent them and maximize the effectiveness, ensure the safety of pharmacotherapy [10].

It is known that the effect of drugs in the body is directly related to its therapeutic concentration, which must be created not only in the blood, but also in target cells [11, 17]. The MDR-1 gene (multidrug-resistance gene) is a gene of multidrug resistance, is the main gene regulating the creation of the necessary intracellular concentration of drugs [9]. The MDR-1 gene promotes binding of the cell to the drug, its entry into the cell, and/or efflux into the intercellular space [4], which explains the development of resistance of the cell to drugs during the expression of this gene. Therefore, the MDR1 gene plays an important role in the effectiveness of pharmacotherapy of various diseases, including chronic gastritis (HCG).

The MDR-1 gene, also called ABC-1, is located on the seventh chromosome and encodes the protein P-glycoprotein (Pgp, translated from the English "permeability" means "permeability"), which is located in the membrane of many normal cells of organs and tissues of the body and regulates the processes of active absorption of drugs through the membrane into the cell [2, 6]. The expression of this protein determines the pharmacokinetics of drugs and, at one time, the effectiveness of pharmacotherapy [5, 15].

The Pgp protein has been detected in the membrane of many organs and tissues of the body: in the liver, it is located on the surface of liver cells and it is contained by small biliary ducts of the liver on its apical surface; also found on the same surface of enteral epithelial cells and colon cells; also, in the kidneys, it is located on the membrane of proximal tubules and found on the apical surface pancreatic small ducts [7]. Pgp is also located in the endotheliocytes of the BBB, as well as such histohematic

barriers as hematovarial and hematotesticular, in addition, it is located in the hematoplacental barrier [3]; and in the immune system it is detected in mature macrophages, in T- and B-lymphocytes, in killer cells of this system and monocytic cells; also in the adrenal glands it is in epithelial cells of the cortex [12].

Currently, more than 100 variations have been described, that is, polymorphisms of the MDR-1 gene [16], but the C3435T polymorphism of this gene is the most studied, so scientists prefer this particular polymorphism. According to world statistics, the noted polymorphism of the MDR-1 gene is detected in 50-60% of Caucasians, 40-50% of Asians, as well as in 10-30% of Africans [8]. It should be noted that the occurrence of polymorphisms of this gene has an ethnic character [2] as well as all genes in general. This fact is explained by multiple allelism - the main factor underlying ethnic genetic differences, which is due to various polymorphic markers of genes [14, 21]. The modern direction of pharmacology is pharmacogenetics, which deals with the individualization of pharmacotherapy, by identifying polymorphic markers that contribute to the body's response to the effects of drugs and changing this reaction. Also, pharmacogenetics provides for the identification of allelic variants of polymorphic markers of the gene involved in drug metabolism in the patient using methods of genotyping the patient and the development of these methods with their widespread introduction into practical medicine [17].

It was found that one of them, the synonymous single nucleotide polymorphism C3435T (silent mutation), is associated with altered functional activity of the P-gp protein [20, 22]. Other polymorphisms occur with the lowest frequency and therefore their influence is not always associated with a change in the functional activity of the Pgp protein.

Based on the above, it should be noted that the widespread prevalence of HCG, especially its associated form with H. pylori, the ineffectiveness of the recommended lines of eradication therapy and the little-studied personal approach to treatment, taking into account the genetic characteristics of a patient with HCG, served as an impetus for us to conduct this study. Therefore, in our opinion, it seems relevant to determine the genetic markers of the prognosis of the formation of therapeutic resistance.

Materials and methods of research

In accordance with the objectives of the dissertation, a planned comprehensive examination of 80 patients with HCG who were on inpatient treatment in the department of gastroenterology and observation in the 1st clinic of the Bukhara OMPKB and in the treatment and diagnostic center "Mohi Hossa" was carried out. These patients were included in the main study group.

The control group included 20 healthy people who had no history of gastrointestinal diseases, who corresponded by gender and age to the main study group - patients with HCG.

The age of patients with HCG ranged from 15 to 79 years, men were 27 (33.8%), women – 53 (66.2%), that is, women significantly prevailed among patients with HCG.

The sampling of biological material in the form of venous blood for DNA extraction was carried out taking into account the established human rights procedure, which was carried out after the examination and with the written consent of the persons included in the study groups (Universal Declaration on the Human Genome and Human Rights (November 11, 1997)).

Genomic DNA was isolated from whole peripheral venous blood. Blood sampling was performed using a vacuum system containing K2-EDTA as an anticoagulant. DNA isolation was carried out in accordance with the instructions of the DNA/RNA isolation kit (Ribot-prep, Interlabservice, Russia) or with the methodology, Mathew S. S., 1984, with some modifications. The isolated DNA was used to carry out a polymerase chain reaction in real time using oligonucleotide primers and allele-specific fluorescent probes using a PCR-RV kit (MANUFACTURED by the company "Syntol" LLC (Moscow, Russia)). FAM and NEX detectors were introduced into the program. The obtained results were documented in the form of growth curves for two FAM and NEX detectors in graphical mode on the corresponding program.

Statistical processing of the results of the study was carried out by a generally accepted method using the Student's criterion

The results of the study

According to the conclusions of scientists of the world, the doctor has an idea of the genotypic affiliation of the patient according to the polymorphisms of the MDR-1 gene makes it possible to choose and dose drugs correctly.

Thus, among patients with H.pylori-associated HCG by polymorphism 3435ST of the MDR-1 gene, 21% had the C/C genotype, about 29% had the T/T genotype and the majority - 59% were patients with the C/T genotype (Fig. 1).

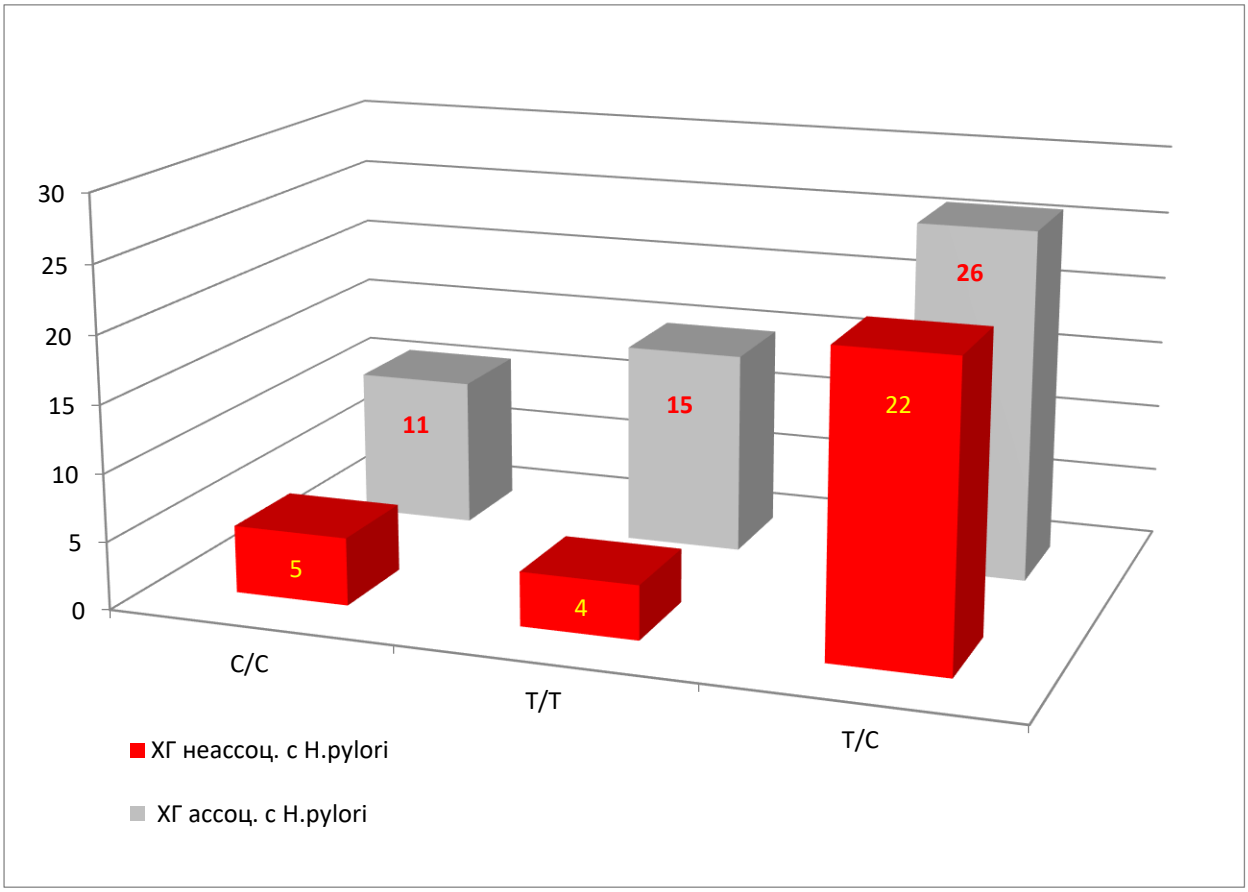

Figure 1. Genotypic variations of patients with H.pylori-associated hCG by polymorphic marker C3435T of the MDR1 gene

When determining the same genotypic affiliation of patients with HCG unassociated with H.pylori, the main part also consisted of patients with the C/T genotype – 42.3%, patients with the C/C genotype made up about 10%, and with the T/T genotype – about 8%.
Thus, patients with HCG with the presence or absence of H.pylori for all polymorphic markers of the MDR1 gene mainly have heterozygous genotypes.

It is known that the polymorphism C3435T of the MDR1 gene has genotypes S/S, T/Thousand/T. After pharmacotherapy, the following treatment results were noted depending on the genotype: in patients with the C/C genotype, recovery, without improvement, deterioration and complications were noted in the same amounts and were 15% each, but improvement was noted in about 39% of patients with a similar genotype (Fig. 2).

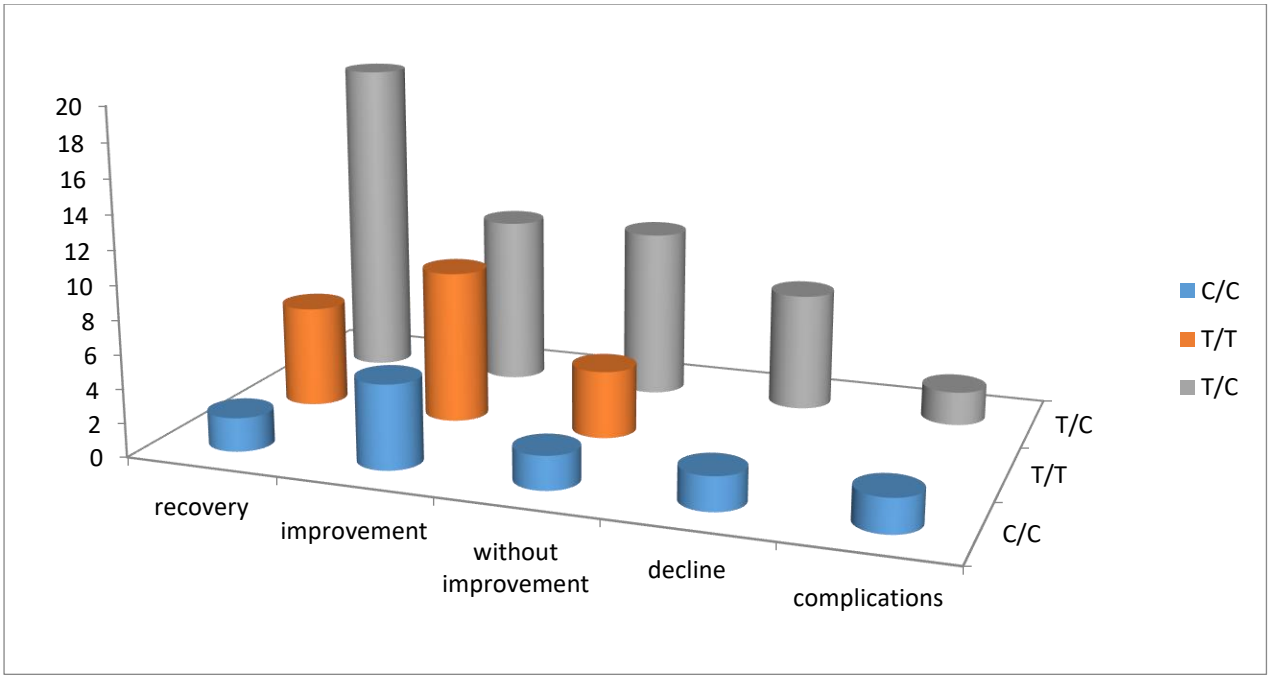

Figure 2. The results of HCG treatment and their relationship with the frequency of distribution of C3435T polymorphism genotypes of the MDR1 gene

It turned out that in patients with the T/T genotype, pharmacotherapy ended in recovery and improvement in 31 and 49% of cases, but in 21% of patients, treatment was without improvement, nevertheless, in patients with a similar genotype, no deterioration and complications were noted.
Patients with the S/T genotype accounted for the main number of patients and recovery occurred in about 40% of cases, but patients with and without improvement after pharmacotherapy accounted for the same number – about 29%; 9% of patients had deterioration and 2% of patients suffered from complications.
Along with the above, the indicators of the need for etiotropic, pathogenetic pharmacotherapy drugs in patients with HCG and for secondary drugs were determined by the genotypes of polymorphism C3435T of the MDR-1 gene. At the same time, according to the polymorphic marker C3435T in patients with the C/C genotype, proton pump inhibitors were used in 63.3% of cases, antibiotics 22.7%, enzymatic drugs 13.6%. In patients with the T/T genotype, proton pump inhibitors were used in 55.3% of patients, antibiotics in 23.7% and secondary drugs in 21% of patients. 50%, 23.9% and 26.1% of these drugs were used in patients with the S/T genotype, respectively (Fig.3).

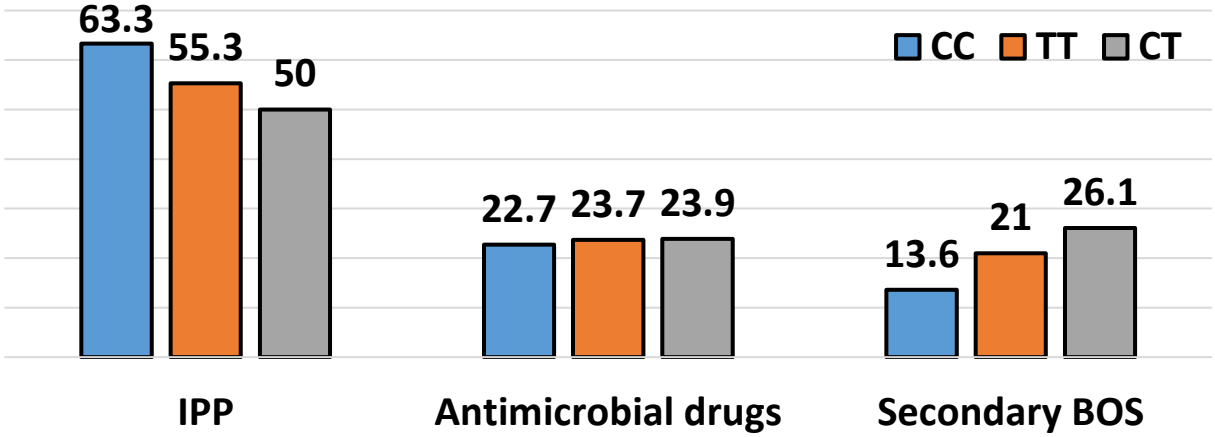

Figure 3. Dependence of etiotropic, pathogenetic and secondary drugs on variants of the genotype of the MDR1 C3435T gene in the structure of treatment of chronic gastritis (%)

Pharmacoepidemiological analysis of all genotypes of the MDR-1 C3435T gene included PPIs and antimicrobials in group A, bismuth preparations and some antibiotics in group B and secondary drugs in group C (Fig. 4).

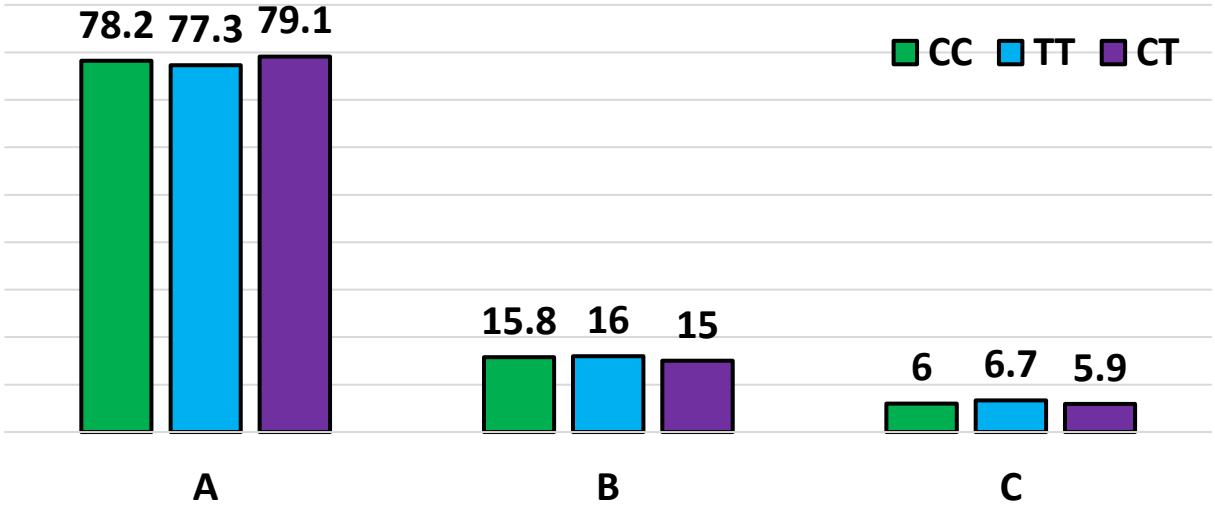

Figure 4. Pharmacoepidemiological analysis of pharmacotherapy of variants of the genotype of the gene MDR1 C3435T in chronic gastritis (%)

Thus, the results of this study are of great importance for the selection of personal dosage regimens of drug pharmacotherapy, which are based on the genotyping of patients. This approach will contribute to improving the effectiveness and safety of HCG pharmacotherapy.

Conclusions. 1**.** The relationship between the types of chronic gastritis, its association with H. pylori, clinical manifestations and genotypes of polymorphisms of the MDR-1 gene, characterized in patients with a "mutant" genotype by pronounced clinical manifestations, association of the disease with H. pylori and a high rate of disease progression, was revealed.

2. After pharmacotherapy, it was noted that in every 1/20 patient the condition remained almost unchanged, in every 1/10 patient the condition worsened, and complications of the disease were observed in every 1/25 patients and more were observed in patients with a heterozygous genotype containing a "mutant" allele of the MDR-1 gene.

3. As part of the complex of drugs for pharmacotherapy of chronic gastritis, the proportion of proton pump inhibitors averaged 53%, antimicrobial drugs averaged 24% and "secondary" drugs averaged 23%.

4. The proportion of etiotropic drugs in the pharmacotherapy of chronic gastritis was highest in patients with the TT genotype of the MDR-1 C1236T gene, and the proportion of pathogenetic treatment — in patients with the CC genotype of the MDR-1 C3435T gene. "Secondary" drugs were more often used in patients with heterozygous genotypic variants of MDR-1 polymorphisms.

Thus, the data obtained by us from clinical and molecular genetic studies of HCG are of great importance in the development of the concept and selection of drugs, and for the selection of personal dosage regimens of drug pharmacotherapy, which are based on the genotyping of patients. This approach will contribute to improving the effectiveness and safety of HCG pharmacotherapy.

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