ISSN 3060-4567

THE RELATIONSHIP OF H.PYLORI BACTERIAL GENOTYPES WITH GENOTYPES

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Abstract *The article reveals the results of a study of the relationship of the genotypes of the virulent gene Ice A of H.pylori bacteria with the genotypes of the gene CYP2C19 of patients with acid-dependent diseases of the digestive system and their effect on the results of pharmacotherapy of acid-dependent diseases of the digestive system, such as gastroesophageal reflux disease, chronic gastritis and peptic ulcer of the stomach and duodenum. Recommendations for personification of pharmacotherapy of acid-dependent diseases of the digestive system are indicated, taking into account the genotypes of the patient and H.pylori bacteria.*

Keywords: *virulent gene IceA 1 N.pylori, genotypes, acid-dependent diseases of the digestive system, pharmacotherapy, personification of pharmacotherapy, gene CYP2C19, drug pharmacokinetics genes.*

INTRODUCTION

Based on modern concepts, H.pylori is not only one of the most common pathogenic bacteria, but also one of the leading aggressive factors in the pathogenesis of acid–dependent diseases [1, 14, 17]. The genome of H. pylori contains genes associated with increased pathogenicity of the microorganism — vacA, CagA, iceA, babA [7, 2, 9]. Their presence is associated with the development of the most significant diseases of the stomach: from gastroesophageal reflux disease, chronic gastritis, gastric and duodenal types of peptic ulcer disease, up to stomach cancer [8, 12, 16]. One of the main pathogenicity factors is the cytotoxicity gene — iceA (induced by contact with epithelium), activated by contact with epithelial cells of the gastric mucosa, which

has two allelic forms — iceA1 and iceA2. Scientists of the world believe that patients infected with H. pylori with the iceA1 genotype have higher infiltration of their own plate of the gastric mucosa by polymorphonuclear neutrophils than those infected with another genotype. There is evidence indicating that the iceA1 allele is more common in peptic ulcer disease, and iceA2 is associated with gastritis [2, 11, 15].

Eradication of H. pylori infection is of great importance for the restoration of a normal lifestyle of a patient with gastrointestinal diseases. To eradicate H. pylori bacteria, gastroenterologists of the world use the recommendations of Maastricht V and the Kyoto Consensus. According to the Maastricht Agreements, after the application of eradication therapy, it is considered effective if the degree of H. pylori eradication reaches at least 80%. However, if during the initial application of eradication schemes the effectiveness reached the necessary figures, then recently there has been a decrease in the effectiveness of therapy to 65-75%. Among the many reasons for the ineffectiveness of pharmacotherapy, researchers point to the genetic characteristics of the patient, which are noted as the main reason not only for the decrease in the effect of therapy, but also for the development of side effects of drugs [3, 6].

It is known that almost all pharmacological agents, being substrates of cytochrome P-450, have corresponding isoforms of this system, which, being inhibitors or inducers in activity, differ from each other only in substrate specificity [4]. It should be noted that the genes encoding these enzymes occupy a special place in the process of biotransformation of drugs, therefore the genetic variability of the genes involved in this process directly affects the manifestation of individual sensitivity to pharmacological agents [5]. The CYP2C19 gene encodes a member of the cytochrome P450 enzyme superfamily, which is an important phase I enzyme widely expressed in endothelial and smooth muscle cells. The enzyme is localized in the endoplasmic reticulum and is a monooxygenase – an enzyme that catalyzes the addition of one oxygen atom. This enzyme participates in the metabolism of many drugs, the synthesis of cholesterol,

steroids and other lipids. Mutations in the CYP2C19 gene can lead to a change in the activity of the enzyme encoded by it [13].

It is known that polymorphisms of the CYP2C19 gene are manifested by three main phenotypic variants of metabolizers. The first is the extensive type, characterized by the normal course of metabolic processes of pharmacotherapy drugs. The second variant of the phenotypic manifestation includes slow metabolizers, which are also called "zero", since they are synthesized defective and therefore the metabolism of the drugs used is reduced. Therefore, either reduce the dose of the drug, or change it to another drug. And finally, the third variant of the phenotypic manifestation is rapid metabolizers, where the metabolism of the drugs used is increased and it is difficult to achieve the desired dose of the drug in the tissue, as a result of which it is recommended to increase the dose of the drug compared with normal metabolizers [5].

Based on the above, it should be noted that the widespread prevalence of acid-dependent diseases, especially its associated form with H. pylori, the ineffectiveness of the recommended lines of eradication therapy and the poorly studied personal approach to treatment, taking into account the genetic characteristics of patients with acid-dependent diseases, served as the impetus for our study. Therefore, in our opinion, it seems relevant to determine the genetic markers of the prognosis of pharmacotherapy of acid-dependent diseases.

The aim of this study was to study the relationship of the genotypes of the virulent gene Ice A of H.pylori bacteria with the genotypic features of the polymorphism G681A of the gene CYP2C19 of patients with acid-dependent diseases in the form of gastroesophageal reflux disease, chronic gastritis, peptic ulcer disease and their effect on clinical manifestations, as well as the results of pharmacotherapy of these diseases.

MATERIALS AND METHODS

A comprehensive examination of 120 patients with acid-dependent diseases was carried out, of which 37 patients with gastroesophageal reflux

disease, 43 patients with chronic gastritis and 40 patients with peptic ulcer disease who were hospitalized in the gastroenterology department and monitored in the 1st clinic of the Bukhara Regional Multi-profile Clinical Hospital and in the treatment and diagnostic center "Mohi Hossa". These patients were included in the main study group.

The control group included 42 healthy people who had no history of gastrointestinal tract disease, who corresponded by gender and age to the main study group.

The age of patients with acid–dependent diseases ranged from 18 to 79 years, men were 74 (62%), women - 46 (38%), that is, men significantly prevailed in the sample of patients with acid-dependent diseases.

In the course of molecular genetic studies, biological material was taken from the stomach of patients in the form of a biopsy to isolate the DNA of H. pylori bacteria. The collection of material and extraction of genomic DNA from the peripheral blood of patients was carried out taking into account the established human rights procedure, which was carried out after a medical examination with the written consent of the subjects (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- Ethylenediaminetetraacetic acid 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. Genotyping of DNA samples by the CYP2C19 gene was carried out by real-time PCR using oligonucleotide primers and allele-specific fluorescent probes using a PCR-RV kit (manufactured by Syntol LLC (Moscow, Russia)). Real-time PCR amplification was performed using a standard protocol. For real-time PCR amplification, Dt lite 4 Real-Time PCR with a 48-cell block was used. 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.

RESULT AND DISCUSSION

Science knows that the virulent gene IceA of H.pylori bacteria has 3 genotypic variants: IceA1/IceA1, IceA1/IceA2 and Ice A2/Ice A2. When studying the comparative characteristics of the occurrence of genotypic variants of H.pylori bacteria in patients with acid-dependent diseases, it turned out that in patients with gastroesophageal reflux disease, the genotype Ice A1/Ice A1 occurs about 65%, while the genotypes Ice A1/Ice A2 and Ice A2/Ice A2 are detected within 15% and 20% (fig. 1).

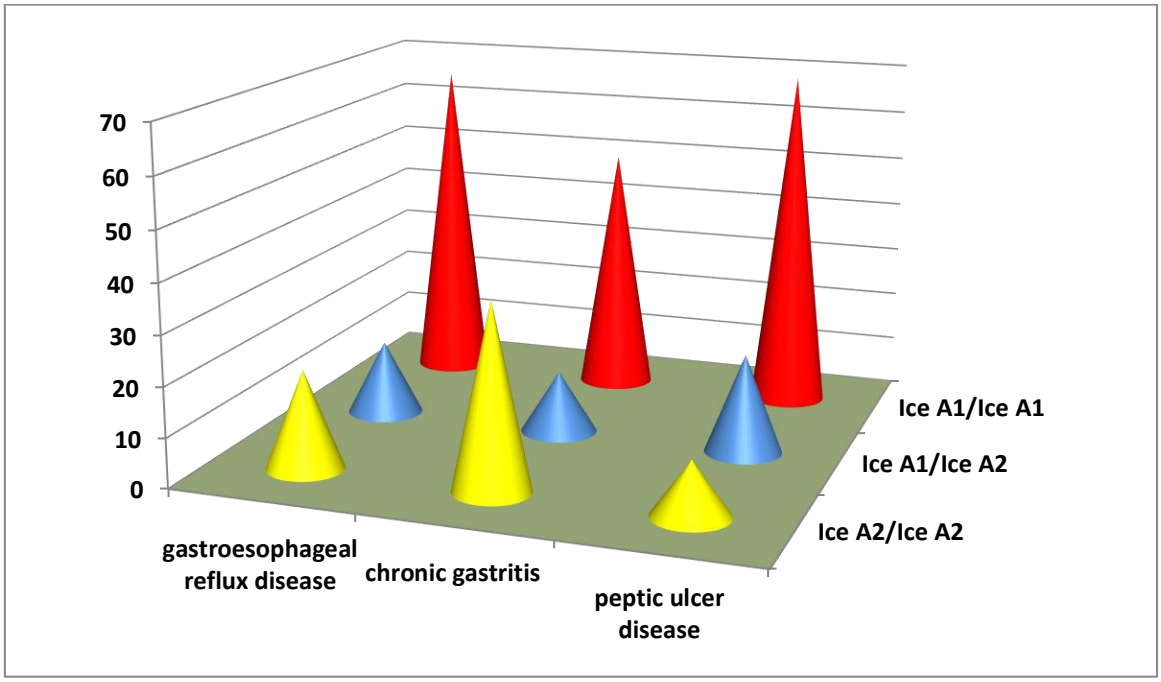

Figure 1. Frequency of occurrence of virulent gene genotypes Ikea H.pylori bacteria in patients with acid-dependent diseases (%)

In addition, in patients with chronic gastritis, the studied genotypic variants of the virulent gene Ice A of H.pylori bacteria were determined in the following order: genotype Ice A1/Ice A1 in every second patient, genotype Ice A1/Ice A2 in every seventh patient and genotype Ice A2/Ice A2 in every third patient. Also, in patients with peptic ulcer disease, the genotype of Ice A1/Ice A1

was determined in the largest number – about 69%, while the genotype of Ice A1/Ice A2 in 20% and the genotype of Ice A2/Ice A2 in 11% of cases.

It is known that eradication therapy includes drugs from the group of proton pump inhibitors, in the metabolism of which the CYP2C19 gene plays a major role. Polymorphism G681A of this gene is characterized by genotypes containing the normal-"wild" allele genotype GG(CYP2C19*1/*1), "mutant" allele genotype AA(CYP2C19*2/*2) and containing "wild" and "mutant" alleles heterozygous genotype GA(CYP2C19*1/*2).

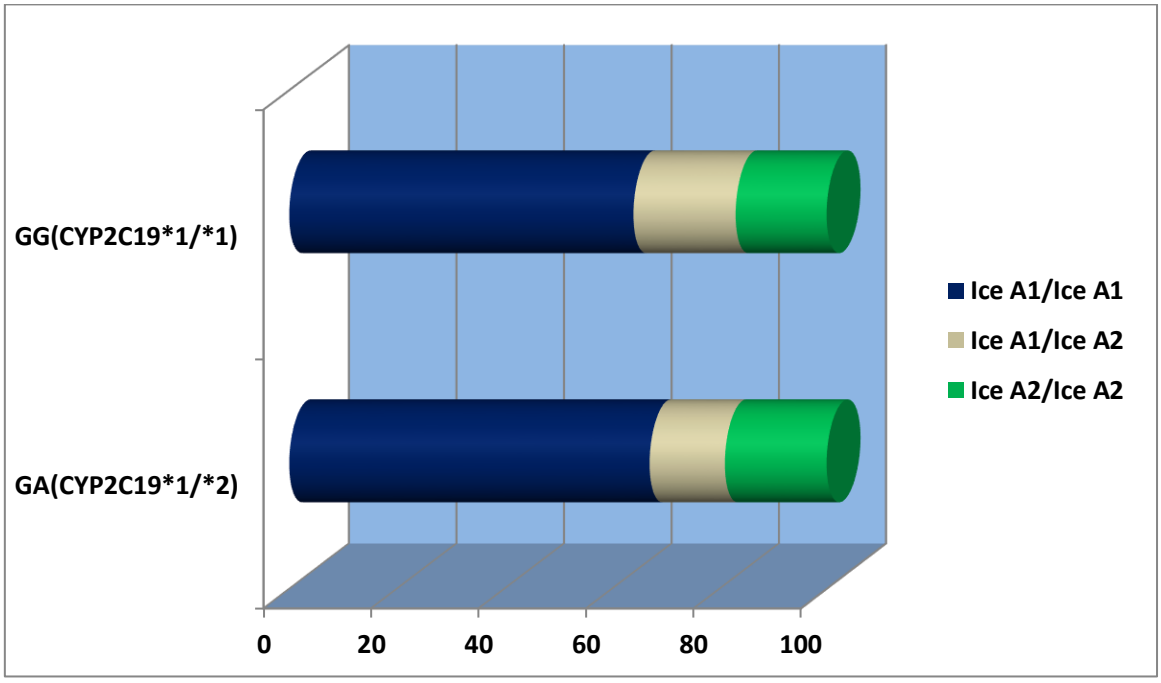

Figure 2. Occurrence of virulent gene genotypes Ikea of H.pylori bacteria in relation to the genotypes of the G 681 A polymorphism of the CYP2C19 gene in patients with acid-dependent diseases (%)

The results of the study showed that in patients with the GG genotype containing the normal-"wild" allele (CYP2C19*1/*1) the presence of H.pylori infection with the Ice A1/Ice A1 genotype was 64%, with the Ice A1/Ice A2 genotype – 19% and with the Ice A2/Ice A2 genotype – about 17% (Fig. 2). And in patients with the heterozygous GA genotype containing "wild" and "mutant" alleles(CYP2C19*1/*2) the presence of the studied bacterial genotypes was in 67%, 14% and 19% of cases, respectively. It should be noted that in the sample

of patients with acid-dependent diseases containing the "mutant" allele genotype AA (CYP2C19*2/*2) has not been identified.

After the eradication pharmacotherapy of acid–dependent diseases, the treatment results were assessed as recovery – in 21% of patients, improvement – in 57% of patients, without improvement - in 16% of patients and complications were noted – in 6% of patients.

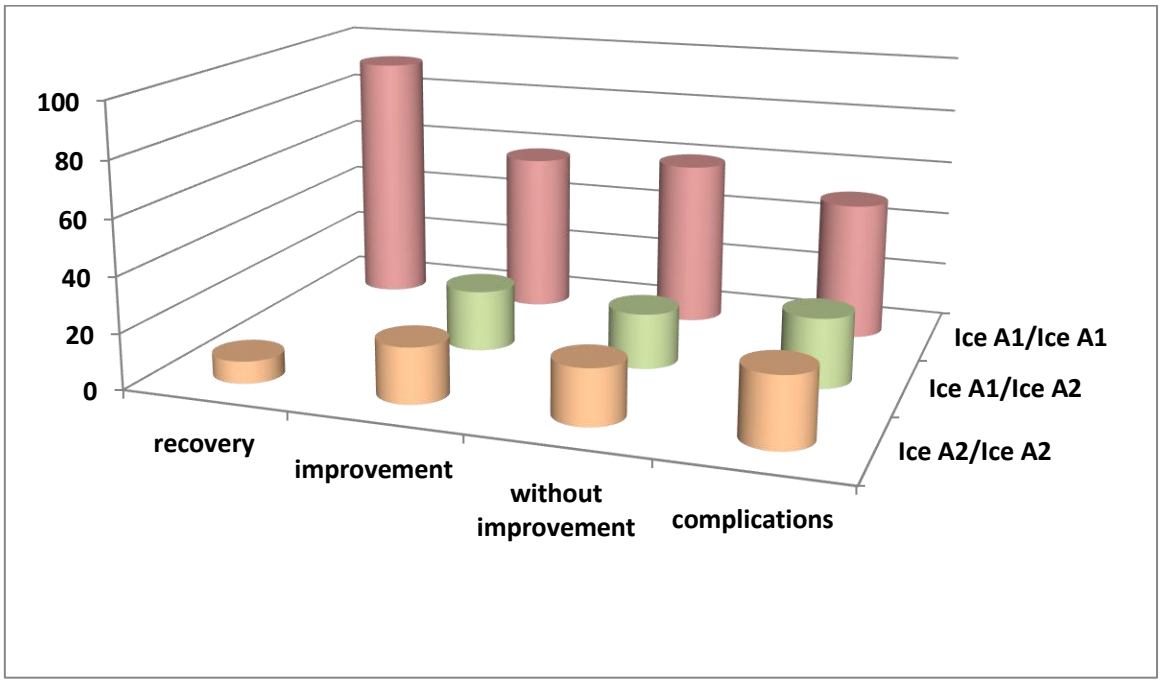

Figure 3. Relationship of genotypes of the virulent gene Ice A H.pylori bacteria with the result of pharmacotherapy of acid-dependent diseases

According to the genotypes of the H.pylori bacterium, these results were characterized as follows (Fig. 3): among patients with recovery in 92% of cases, the presence of the genotype Ice A1/Ice A1 of H.pylori infection was noted, in 8% the presence of the genotype Ice A2/Ice A2 of H.pylori, and the genotype Ice A1/Ice A2 recovery was not characterized; in patients with improvement, the presence of the genotype Ice A1/Ice A1 was detected in 58% of cases, the presence of the genotype Ice A1/Ice A2 infection – in 22% and the presence of the genotype Ice A2/Ice A2 H.pylori – in 20% of cases; in patients without improvement, the presence of the genotype Ice A1/Ice A1 of H.pylori bacteria was detected in 60% of cases and the presence of the other two genotypes in 20%

of cases; in patients with complications, every second genotype of the bacterium Ice A1/Ice A1 was detected, and every fourth patient had the remaining genotypes of H.pylori infection.

CONCLUSIONS

Based on the above, it should be noted that the genotype IceA1/IceA1 of the virulent gene of the bacterium Ice infection H.pylori is detected in patients with acid-dependent diseases to a greater extent than other genotypes of the bacterium. In addition, this genotype of H.pylori bacteria is more often associated with the “wild” allele variant of the G polymorphism G681A of the gene CYP2C19, responsible for the metabolism of proton pump inhibitors - drugs of the main series during the eradication of H.pylori infection. This indicates the influence of the genotypes of both the patient and the bacteria on the results of pharmacotherapy. As it was revealed, in patients with the presence of the IceA1/IceA1 genotype of the virulent gene of the H.pylori infection Ice bacterium, eradication therapy was successful and recovery was in the greatest cases. Thus, the genotyping of both the patient and H.pylori bacteria have individual characteristics, which indicates the personification of pharmacotherapy.

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ISSN 3060-4567

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