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Research Article

Drug Induced Liver Injury in HIV-Infected Patients during Antituberculosis Therapy

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Abstract

Objective: Value of genotyping of cytochrome P450 2E 1 and NAT2 enzymes in prediction of drug induced liver injury (DILI) in patients with pulmonary tuberculosis and in HIV-coinfected patients who are undergoing antituberculosis and antiretroviral therapy.

Materials and Methods: 200 patients were examined during the study. Patients with or without drug-induced liver disease on the background of anti-tuberculosis chemotherapy were studied by genotyping of cytochrome P450 2E 1 and NAT2 enzymes by "real time" polymerase chain reaction (PCR) and 13C-metacetin breath test.

Results: In the 2nd group and in the 4th group (in groups of patients with drug-induced liver disease on the background of anti-tuberculous therapy), slow acetylators and genotype of cytochrome P450 2E 1 c1/c1 prevailed.

Conclusion: It is advisable to recommend patients in the high-risk group for the development of drug-induced liver injury to determine the activity of cytochrome P450 2E 1 and NAT2 enzymes by genotyping and phenotyping in order to select the optimal scheme of anti-tuberculosis therapy, which will lead to increased adherence of patients to therapy and improvement of patients' quality of life.

Keywords: *Human Immunodeficiency Virus; Pulmonary Tuberculosis; DILI-Drug Induced Liver Injury*

Abbreviations

HIV: Human Immunodeficiency Virus; DILI: Drug Induced Liver Injury; TB: Pulmonary Tuberculosis; NAT2: N-Acetyltransferase 2; HAART: Highly Active Antiretroviral Therapy; ALT: Alanine Aminotransferase; AP: Alkaline Phosphatase; PCR: Polymerase Chain Reaction; 13C-MetDT:13C-Metacetin Respiratory Test

Introduction

The global burden of tuberculosis of the Russian Federation, calculated through the indicator of the number of years of life lost from disability and mortality, is about 5 lost years of life per 1 thousand. inhabitants, while in the world this figure is 0.7 years per 1 thousand residents in Germany and France are approaching to 0 [1]. Anti-tuberculosis drugs such as isoniazid, pyrazinamide, ethionamide, protionamide, ethambutol have significant hepatotoxicity [2,3]. In patients receiving anti-tuberculosis treatment, DILI remain the most frequent adverse event. The percentage of DILI in anti-tuberculosis treatment, according to domestic authors, can vary from 10 - 15 to 45% [4,10]. In 11 - 28% of patients, the development of DILI requires the withdrawal of anti-tuberculosis therapy [5], which reduces patients' motivation for treatment and indicators of patients' quality of life.

Pharmacogenetic testing - the most perspective tool for clinical practice of the personalized medicine at which the genetic features of the patient causing "answer" to any given medicine (efficiency/inefficiency/development of adverse collateral reactions) can be revealed.

Aim of the Study

The aim of the study is to individualize therapy in patients with pulmonary tuberculosis and in HIV-co-infected patients on TB and highly active antiretroviral therapy (HAART) by studying risk factors for DILI (polymorphism of NAT2 and cytochrome P450 2E1).

Materials and Methods

The study examined 200 patients. 120 patients diagnosed for first-time pulmonary tuberculosis (TB) and anti -TB therapy were started according to I or III treatment regimen. The average age of patients was 47 ± 13 years.

In 60 patients (50%) out of 120, was verified for first-time HIV infection, however, for a number of reasons, this patients did not receive HAART. In groups of patients with pulmonary tuberculosis and co-infected patients, TB/HIV identified those who developed a DILI on the background of long-term anti-tuberculosis therapy. As a result, in two large groups of patients with TB and TB/HIV co-infection, two subgroups of patients with and without DILI were isolated.

Thus, four equal patient groups were investigated: group 1 - patients with pulmonary tuberculosis (n = 30), group 2 - with TB and developed DILI on of anti-tuberculosis therapy (n = 30), group 3 - patients with HIV and TB lung co-infections (n = 30), group 4 - patients with co-infection of TB/HIV and DILI on of anti-tuberculosis therapy.

The diagnosis of a DILI was based on the presence of a connection between the beginning of anti-tuberculosis therapy and the clinical-laboratory picture of the development liver damage. In carrying out laboratory methods of research, an increase in the level of ALT and/or alkaline phosphatase (AP) of more than 2 norms was determined. During differential diagnosis, acute viral hepatitis were excluded, as well as involvement with hepatotropic viruses: cytomegalovirus and herpes simplex virus. Depending on the predominance of cytolytic or cholestatic syndrome, drug damage to the liver is divided into three forms: hepatocellular, cholestatic and mixed. An R-value is used to determine the form of the DILI. R-value is defined as the ratio of ALT/ALT ULN to AP/AP ULN, where ULN is the upper limit of the norm. Therefore, the cytolytic variant was determined at $R > 5$; cholestatic variant - at $R < 2$; the mixed option - at R from 2 to 5 [6,7].

The patient examination complex included:

- Data from clinical and laboratory studies (ALT, AP, bilirubin);
- Genotyping cytochrome P450 2E1 and NAT2 enzymes (polymerase chain reaction (PCR) in real-time mode);
- 13C-metacetin respiratory test (determination of the mass of functioning hepatocytes; phenotypic determination of cytochrome P450 2E12 and NAT2 enzymes activity) [8].

Results

According to the results of the study, all patients were divided into three groups: fast acetylators - wild-type homozygotes NAT2 * 4 alleles, intermediate and slow acetylators - carriers of a combination of mutant alleles [9,11].

When determining the type of acetylation, it was revealed that in the 2nd group and in the 4th group, slow acetylators (SA) prevailed: 83.3% of patients in Group 2 and 73.3% in Group 4, respectively ($p < 0.05$) compared to Group 1 (26.7%) and Group 3 (33.3%), where no medicinal liver lesions were reported in patients. Fast acetylators (FA) prevailed in the 1st group (26.6%, $p > 0.05$) and the 3rd group

(23.2%, p > 0.05) compared to the 2nd group (10.0%) and the 4th group (12.5%). The genotype with an intermediate type of acetylation (IA) prevailed in the 1st (46.7%, p > 0.05) and 3rd group (43.5%, p > 0.05) (Figure 1). The genotype of cytochrome P450 2E 1 c1/c1 was also determined more frequently in the 2nd (c1/c1-93.3%, c1/c2-6.7%, c2/c2-0%) and 4th groups (c1/c1-96.7%) (Figure 2). When performing 13C-MetDT, the dose/hour in all patients exceeded 14.6%, which indicates the absence of pronounced fibrosis in the study group of patients. The cumulative dose at 120 minute of 13C-MetDT was higher in the 1st and 3rd group (21.0 ± 1.7%, p < 0.05) and (24.3 ± 3.8%, p < 0.05) compared to the 2nd (16.4 ± 3.5%) and 4th (18.0 ± 2.8%) (Figure 3).

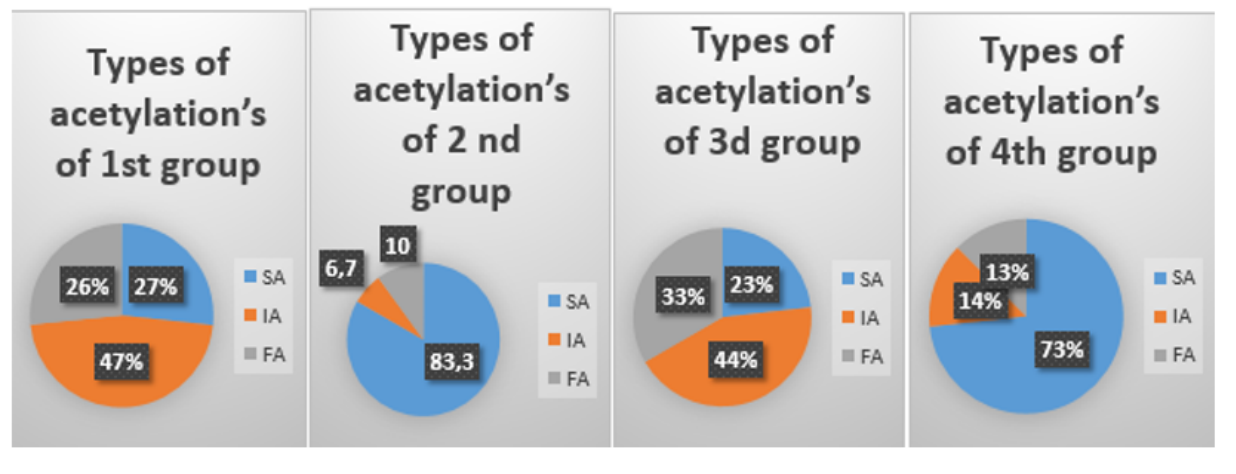

Figure 1: *Types of acetylation's.*

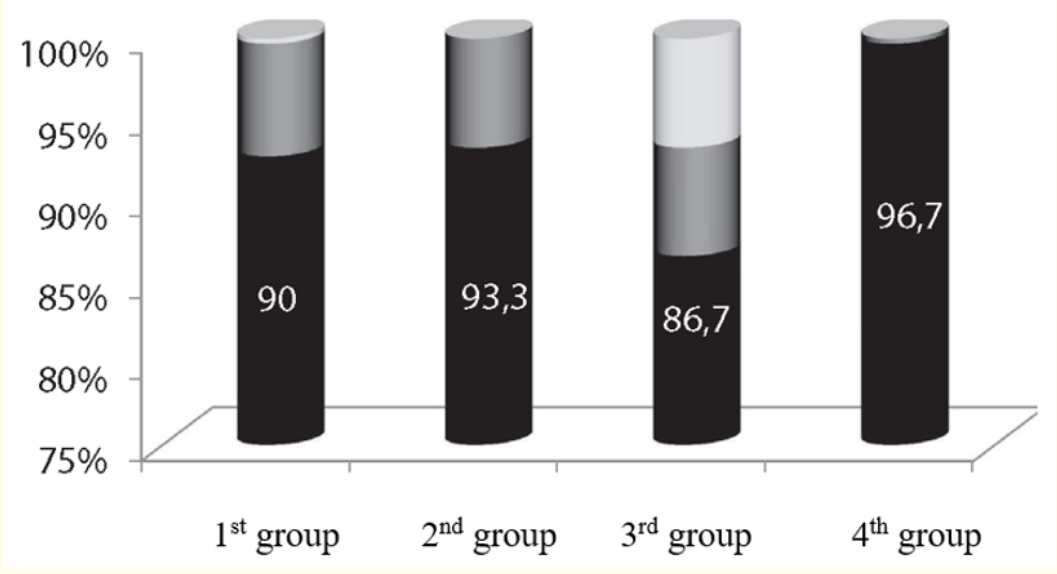

Figure 2: *Percent of c1/c1 type of cytochrome P450 2E 1.*

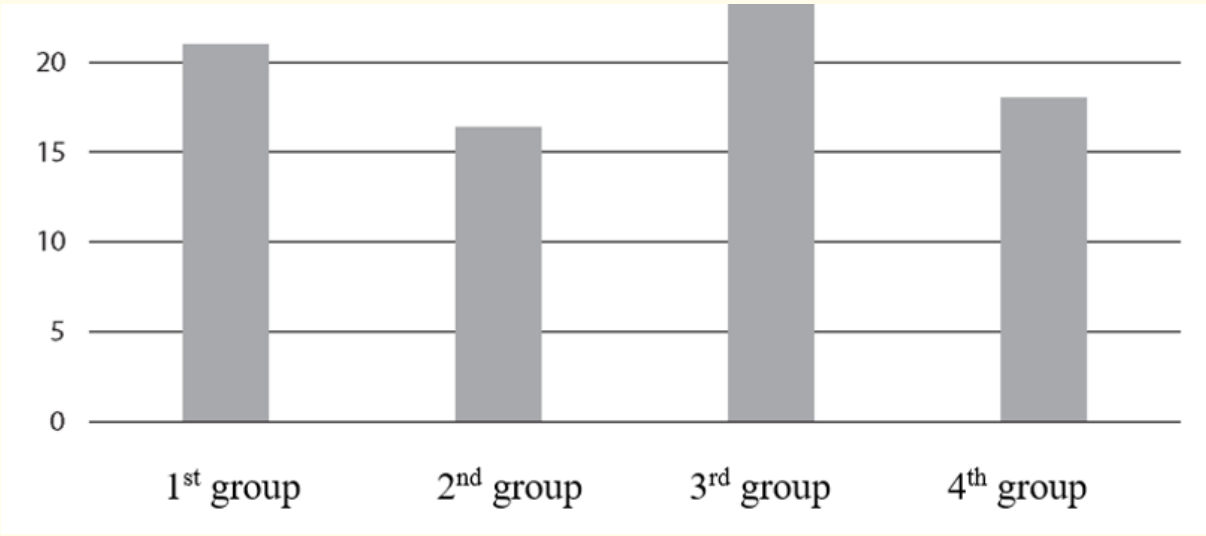

Figure 3: *Cumulative dose at 120 minutes of 13C-MetDT.*

Discussion

Genetically and phenotypically slow acetylators NAT2 and cytochrome genotype P450 2E 1 c1/c1 (according to PCR real-time and 13C-metacetin respiratory test) were associated with a higher risk of DILI in patients with pulmonary tuberculosis and HIV/TB co-infection of the lungs on anti-tuberculosis therapy. Slow acetylators are significantly more likely to develop DILI during anti-tuberculosis therapy. A slow type of acetylation is a risk factor for DILI for both TB and HIV/TB co-infected patients. The 13C-metacetin respiratory test is able to diagnose pronounced fibrosis and cirrhosis of the liver. Coincidence of genetic and phenotypic type determination results acetylation makes it possible to use a 13C-metacetin respiratory test to determine the type of acetylation and diagnose pronounced fibrosis and cirrhosis in patients before prescribing anti-tuberculous therapy, in order to assess the risk of developing DILI.

Conclusion

It is advisable to recommend to patients at high risk for the development of DILI to determine the activity of cytochrome P450 2E1 and NAT2 enzymes in order to choose the optimal regimen of anti-tuberculosis therapy (which will achieve individualization of therapy). It will lead to increased patient adherence to therapy and, therefore, to an increase in the quality of life of patients.

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