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CAN WE ASSESS THE *CYP3A4*1G* POLYMORPHISM AS A PREDICTOR OF THE HEPATOTOXICITY DURING ANTITUBERCULOSIS THERAPY?

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Background

Adverse effects of anti-tuberculosis (TB) agents, which include anti-TB drug-induced liver injury observed in 10%–26% of TB patients who were receiving standard short-course chemotherapy, are the important obstacles for successful TB treatment. The risk of anti-TB drug-induced liver injury could be determined by patients' genotype polymorphism of the xenobiotic-metabolizing enzymes such as cytochrome-4502E1 (CYP2E1), CYP2C9, N-acetyltransferase 2, and glutathione S-transferase etc [1,2]. It is well-known that the CYP3A4 enzyme is responsible for metabolism for almost one-third of all medicines, including anti-TB drugs. The enzymatic activity of CYP3A4 greatly depends on polymorphism of corresponding genes as *CYP3A4*1G, CYP3A4*1B* etc. According to *Miriam Saiz-Rodríguez, et al. 2019*, the presence of a variant allele *CYP3A4*1G* is associated with decreased fentanyl metabolism. Thus, patients' *CYP3A4* genotype polymorphism might have certain impact on the drugs' concentration in the blood and finally on the effectiveness of TB treatment. One can predict that in the individuals with "rapid metabolizer" (RM) genotype, serum drug's concentration would be lower and treatment outcome would be worse than in the carriers of "slow metabolizer" (SM) genotype. For the risk of hepatotoxicity it might be opposite relationship.

The aim of this research was to find the meaning of *CYP3A4*1G* polymorphism in TB patients for the toxicity development during inpatient TB treatment.

Design Method

Blood samples were obtained from 105 patients with newly diagnosed pulmonary TB at Odessa Regional TB Hospital in 2015. The study was approved by Ethical Commission of Odessa National Medical University. DNA material was extracted from the blood using a kit of DNA-Sorb-B. A *CYP3A4*1G* genotype was detected with the help of PCR according to *Yuan Gao, et al. 2008*. All TB patients were receiving complex therapy recommended by the World Health Organization DOTS strategy. We have considered medical records at the beginning and at the end of inpatient treatment including activity of biochemical indices such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutathione transferase (GGT), and total bilirubin level in blood serum.

The project was conducted according to the Declaration of Helsinki standards. All of the patients gave written informed consent and explicitly provided permission for treatment and blood analyses, as well as for the collection of relevant clinical data.

Statistical analysis was performed using the "Primer Biostatistic" package (Kruskal–Wallis and ANOVA tests). The Chi-square test was used to determine whether there is a significant difference concerning frequency of studied criteria between two groups. Statistical significance was assumed at the $P < 0.05$.

Results

*CYP3A4*1G* genotyping of 105 patients has shown that 91.4% had no mutation in this region (**1/*1* genotype; "rapid metabolizers"), 4.8% had one mutated allele (**1/*1G* genotype; "intermediate metabolizers"), and 3.8% had both mutated alleles (**1G/*1G* genotype; "slow metabolizers"). At the beginning of the treatment the level of studied biochemical indices was almost the same regardless of *CYP3A4*1G* genotype. After the conducted in-patient treatment in "rapid metabolizers" studied biochemical indexes insignificantly increased, while the level of bilirubin has dropped on 10,4% (p=0,023; CI=-2,85…-0,21). In "slow metabolizers" after inpatient treatment the serum total bilirubin level increased on 8,0% (p<0,001; CI=2,33…6,03), the activity of ALT raised on 67,2% (p=0.033; CI=-30,14…-1,86), AST - on 37,4% (p>0,05) comparatively to the initial level; also the amount of the patients with ALT and AST level beyond normal almost doubled. In result of inpatient treatment in "intermediate metabolizers" the activity of serum ALT and AST increased in 1.5 times (p>0,05). After completion of inpatient treatment in "intermediate metabolizers" and in "slow metabolizers" serum GGT activity increased in 2,5 times (p<0,05) and 1,3 times (p>0,05) correspondently; among "rapid metabolizers" – on the contrary, the number of the individuals with increased GGT level has dropped (p<0,05). According to obtained results the presence of variant alleles ("slow metabolizers" genotype) is accompanied by slowing down of the conjugation stage rate in liver that is approved by increasing of bilirubin level. In addition, this genotype is associated with more intensive cytolysis of hepatocytes that is witnessed by raising of ALT and ACT activity in the blood.

Conclusions

Thus according to *CYP3A4*1G* genotype after completion of in-patient stage of anti-TB treatment the intensity of cytolysis and hepatotoxicity indices in "slow metabolizers" were much higher than in "rapid metabolizers". That is why, the detection of *CYP3A4*1G* genotype in TB patients at the beginning of TB treatment could help to recognize the individuals with high risk of liver injury who need additional medical care.

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