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PROGNOSTIC VALUE OF *CYP3A4*1B* POLYMORPHISM IN PATIENTS WITH PULMONARY TUBERCULOSIS

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Introduction. Previously it was found that in *slow metabolizers* according to *CYP3A4*1G* genotype after completion of in-patient stage of anti-tuberculosis treatment, the level of cytolysis and toxicity indexes was much higher than in *rapid metabolizers*. **The aim of the present research** was to find the meaning of *CYP3A4*1B* polymorphism in tuberculosis (TB) patients for the level of isoniazid and rifampicin as well as for the outcome and toxicity development during in-patient TB treatment.

Materials and methods. The medical records of 105 patients with pulmonary tuberculosis were examined. All these patients had primary pulmonary tuberculosis. They were receiving in-patient treatment at the Odesa Regional Center for Socially Significant Diseases (previously – the Odesa Regional Tuberculosis Dispensary) in 2012–2014. The study was conducted under the Declaration of Helsinki standards.

Results. After in-patient treatment, the activity of cytolysis markers as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and the cholestasis marker as gamma-glutathione transferase (GGT) in TB-patients with **AA* genotype increased insignificantly by 7.0%, 9.3%, and 4.5% ($p>0.05$); in patients with the **AG* genotype, the activity of ALT, AST and GGT, on the contrary, had a tendency for decreasing – by 18.7%, 3.0% and 9.0% ($p>0.05$); a similar trend was observed concerning the number of patients with increased activity of ALT, AST and GGT. At the end of treatment, the average activity of ALT in carriers of the **AA* genotype was 1.8 times higher than in carriers of the **AG* genotype ($p=0.046$; CI=-0.26...22.24).

Conclusion. At the beginning of anti-tuberculosis chemotherapy, it is recommended to determine the *CYP3A4*1B* genotype in patients with pulmonary tuberculosis, which allow identifying the groups of patients with the **AG* genotype, which is characterized by a greater risk of developing sub-therapeutic rifampicin concentrations in the blood during treatment and prove the usefulness of personalized choice of rifampicin dosage according to the *CYP3A4*1B* genotype.

Key words: *CYP3A4*, tuberculosis, rifampicin, genotype, polymorphism.

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ПРОГНОСТИЧНЕ ЗНАЧЕННЯ ПОЛІМОРФІЗМУ *CYP3A4*1B* У ХВОРИХ НА ТУБЕРКУЛЬОЗ ЛЕГЕНЬ
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Метою дослідження стало вивчення комплексного впливу поліморфізму локусу *CYP3A4*1B* на вміст найбільш ефективних протитуберкульозних препаратів, ефективність та токсичність протитуберкульозної терапії. Хворі з генотипом **AG* локусу *CYP3A4*1B* через 2 і 6 год. після введення рифампіцину в 5 і 10 разів частіше мали субтерапевтичну концентрацію рифампіцину відповідно, ніж носії генотипу **AA* ($p<0.05$); після стаціонарного лікування у носіїв генотипу **AG* активність АлТ, АсТ і ГГТ дещо знизилась – на 18,7, 3,0 і 9,0% відповідно ($p>0.05$), водночас у носіїв генотипу **AA* недостовірно зросла – на 7,0, 9,3 і 4,5% відповідно ($p>0.05$). Процес туберкульозного обсіменіння легеневої тканини у носіїв генотипу **AG* зберігався втричі частіше, ніж у групі **AA* ($p<0.05$). Таким чином, визначення генотипу *CYP3A4*1B* у хворих на туберкульоз легень на початку лікування дасть змогу індивідуально підбирати дозу рифампіцину.

Ключові слова: *CYP3A4*, туберкульоз, рифампіцин, генотип, поліморфізм.

Introduction. According to WHO, 2021, Ukraine belongs to the countries with a significant spread of multi-drug resistant strains of *M. tuberculosis* [1]; additionally, military aggression against Ukraine complicates anti-tuberculosis control in Ukraine [2]. It is known that multi-drug resistant strains of *M. tuberculosis* more often belong to the *Beijing* family and lead to worse tuberculosis (TB) treatment outcome; infection with *Beijing* strains of *M. tuberculosis* can be considered as one of the unfavorable disease course factors [3; 4]. Adverse effects of anti-TB agents, which include anti-TB drug-induced liver injury observed in 10%–26% of TB patients who had standard short-course chemotherapy, are the important obstacles for successful TB treatment [5]. 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), N-acetyltransferase 2, and glutathione S-transferase [6, 7]. In addition, the above-mentioned enzymes play an important role in biotransformation of the anti-TB drugs. So, patients' genotype polymorphism has certain impact on the drugs' concentration in the blood and finally on the effectiveness of TB treatment. For example, TB patients with "*slow metabolizers" (SM)* genotype of *CYP2C9* gene had the highest serum isoniazid and rifampicin level and the most favorable treatment outcome comparatively to "*rapid metabolizers" (RM)* genotype group [8]. According to *CYP3A4*1B* genotype in TB patients with *RM* genotype, the indexes of cytolysis (alanine aminotransferase, aspartate aminotransferase and bile stasis (gamma-glutathione transferase) were higher comparatively to *SM* genotype both before and after in-patient treatment [9]. According to the literature, the enzyme cytochrome (CYP) 3A4/5 is involved in the metabolism of more than a one-third of all drugs [10]. The activity of the enzyme is largely determined by the polymorphism of the corresponding *CYP3A* genes [10]. *CYP3A4* genetic polymorphism was accompanied by differences in the mRNA level. Carriers of the *CYP3A4*AA* genotype had the most pronounced analgesic effect in case of transdermal application of buprenorphine. The presence of variant *CYP3A4* alleles can affect methadone metabolism, and rather it is a question of the effect of a combination of single nucleotide polymorphisms (SNPs) than a single *CYP3A4* polymorphism. The presence of *rs2242480* and *rs2740574* polymorphisms might play a key role in increasing the risk of death in methadone use [11]. Previously it was found that in *slow metabolizers* according to *CYP3A4*1G* genotype after completion of in-patient stage of anti-TB treatment the level of cytolysis and toxicity indexes was much higher than in rapid metabolizers [12]. **The aim of the present research** was to find the meaning of *CYP3A4*1B* polymorphism in TB patients for the level of isoniazid and rifampicin as well as for the outcome and toxicity development during in-patient TB treatment.

Materials and methods. The medical records of 105 patients with pulmonary tuberculosis were examined. All these patients were diagnosed tuberculosis for the first time (primary tuberculosis). They were receiving in-patient treatment at the Odesa Regional Center for Socially Significant Diseases (previously – the Odesa Regional Tuberculosis Dispensary) in 2012–2014. All tuberculosis patients received standard therapy according to the order of the Ministry of Health of Ukraine No. 384 dated 06.09.2006. The project was approved by the Ethics Committee of the Odesa National Medical University, Odesa, Ukraine. The study was conducted under the Declaration of Helsinki standards.

DNA material was extracted from the blood using a kit of DNA-Sorb-B. A *CYP3A4*1B* genotype was detected with the help of polymerase chain reaction (PCR) and endonuclease analysis [13]. All TB patients were receiving complex therapy including rifampicin and isoniazid orally about 8–12 and 4–6 mg/kg of body weight per day (totally 450–600 and 300–400 mg), respectively in combination with pyrazinamide (20–30 mg/kg), streptomycin (12–18 mg/kg) or ethambutol (15–20 mg/kg) according to the order of Ministry of Health of Ukraine No. 384 and recommended by the World Health Organization DOTS strategy. We have considered medical records at the beginning and at the end of in-patient treatment including TB form, characteristics of TB lesions, smear status, activity of biochemical indices such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutathione transferase (GGT) which were measured on the HumaStar300 automatic analyzer ("Human GmbH," Germany).

The blood samples were collected from TB patients during the first 2 weeks of in-patient treatment 2, 4, 6, and 24 h after administration of rifampicin and isoniazid. The level of rifampicin was determined according to Chubaryan method with modification that is based on the extraction of rifampicin from the blood using chloroform and KON with further spectrophotometric analysis of the extract at 470 nm [8]. The content of isoniazid was determined according to the method of Wallenberg in modification of Shenderov [8]; isoniazid forms a colored complex with vanadium-acidic ammonia in the acidic medium; the intensity of coloring can be measured at a wavelength of 400 nm.

Statistical analysis was performed using the Statistica 10.0 software (Dell Software, Austin, TX, USA) with parametric and non-parametric methods (ANOVA and Kruskal–Wallis 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*1B* genotyping of 105 patients has shown that 96 individuals (91.4%) had **AA* genotype (*"rapid metabolizers"*), the rest 9 individuals (8.6%) had **AG* genotype (*"moderate metabolizers"*). No individual was found to have homozygous variant genotype **GG* (low enzymatic activity or "*slow metabolizers"*). According to previous research in Odesa region in healthy individuals (control group) 93.7% were carriers of **AA* genotype (*"rapid metabolizers"*), 6.3% – carriers of **AA* genotype (*"moderate metabolizers"*).

According to the obtained data, there were no significant differences in the concentration of rifampicin in patients with pulmonary TB regarding to the *CYP3A4*1B* polymorphism (Table 1). At the same time, a slightly higher concentration of rifampicin was observed in carriers of the **AA* genotype than in carriers of the **AG* genotype.

Table 1

Serum rifampicin concentration regarding to *CYP3A4*1B* polymorphism in TB-patients

Genotype of *CYP3A4*1B*	Serum rifampicin concentration (mg/kg) after drug's administration (Mean±SED)			
	2 hrs	4 hrs	6 hrs	24 hrs
**AA* (n=37)	11.79±2.53	16.25±3.92	11.01±2.04	7.26±1.60
**AG* (n=6)	11.05±0.48	15.03±0.97	9.50±0.64	6.79±1.20

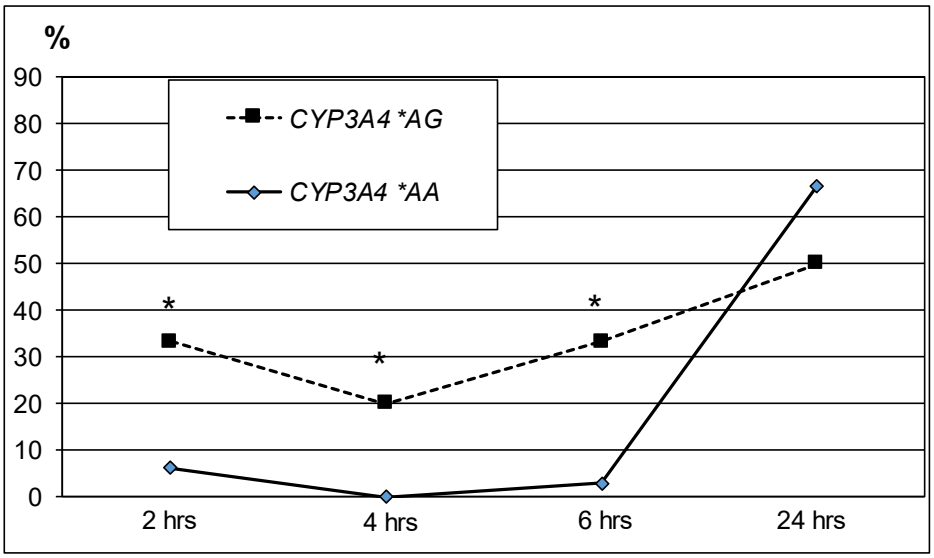
The percentage of patients with different *CYP3A4*1B* genotypes with concentration of rifampicin was lower than the minimal therapeutic concentration (Fig. 1).

During 2–6 hrs after drugs' administration, 7% of patients with the **AA* genotype had a concentration lower than the minimal therapeutic concentration. In a day after rifampicin administration, about two-thirds of the patients had a sub-therapeutic concentration of the rifampicine.

In carriers of the **AG* genotype, the number of patients with a subtherapeutic concentration ranged from 20% 4 hrs after administration to 50% a day after administration; the number of patients with **AG* genotype with subtherapeutic concentration 2 hrs after administration was 5 times more often than carriers of the **AA* genotype (χ^2=3.94, with a critical value of χ^2=3.84; p<0.05); 4 hrs after administration – by 20% more often (χ^2=6.58; p<0.05); 6 hrs after administration – almost 10 times more often (χ^2=6.57; p<0.05) than carriers of the **AA* genotype.

There were no significant differences of isoniazid concentration between different *CYP3A4 *1B* genotypes (Table 2). At the same time, a slightly higher concentration of isoniazid in the blood was observed in carriers of the **AA* genotype than in carriers of the **AG* genotype.

At the beginning of in-patient treatment, TB-disintegration processes were observed in approximately 45.8% of "*rapid metabolizers"* (genotype **AA*) and more than in half of "*moderate metabolizers"* (genotype **AG*) – 55.6%. Among carriers of the **AA* genotype, the processes of disintegration and dissemination appeared in 13.5% and 32.3% TB-patients, respectively; at the same time, in TB-patients with the **AG* genotype, the specified processes were observed in 44.4% of individuals (Table 3).



* – p<0.05 (relatively to **AA* genotype)

Fig. 1. Number of tuberculosis patients that did not reach recommended rifampicin concentration in the blood after different time interval concerning *CYP3A4*1B* polymorphism

Table 2

Serum isoniazid concentration regarding to *CYP3A4*1B* polymorphism in TB-patients

Genotype of *CYP3A4*1B*	Serum isoniazid concentration (mg/kg) after administration (Mean±SED)			
	2 hrs	4 hrs	6 hrs	24 hrs
**AA* (n=37)	4.16±0.20	2.57±0.23	1.34±0.19	0.18±0.06
**AG* (n=6)	4.06±0.44	2.16±0.42	0.88±0.21	<0.023

Table 3

Description of pulmonary TB-lesions regarding to CYP3A4*1B polymorphism

Characteristics of TB-lesions	At the beginning of in-patient treatment, (%)		At the end of in-patient treatment, (%)	
	**AA*, n=96	**AG,* n=9	**AA*, n=96	**AG,* n=9
Infiltration	52 (54.2)	1 (11.1)*	9 (9.4)#	-
Disintegration	13 (13.5)	4 (44.4)*	-#	-#
Dissemination	31 (32.3)	4 (44.4)	9 (9.4)#	3 (33.3)*
Resorption	–	–	78 (81.2)#	6 (66.7)#

Note:

1. # – p<0.05 (relatively to the initial level of correspondent group);

2. * – p<0.05 (relatively to the patients with **AA* genotype).

In addition, in carriers of the **AG* genotype, disintegration processes occurred 3.3 times more often than in carriers of the **AA* genotype ($p<0.05$; $\chi^2=5.79$ with a critical value of $\chi^2=3.84$ hereafter). On the other hand, infiltration processes were most common in individuals with the **AA* genotype – 54.2% that is almost 4.9 times more often than in patients with the **AG* genotype – 11.1% ($p<0.05$; $\chi^2=6.10$). So, at the beginning of treatment, TB-patients who had the **AG* genotype had somewhat more frequent destruction and disintegration processes in the lungs than carriers of the **AA* genotype.

At the beginning of in-patient treatment, about half of carriers of the **AA* genotype, according to microscopy, were smear-positive, while 77.8% of **AG* were smear-positive (Fig. 2).

According to culture, the majority of the patients – 66.7% of "*rapid metabolizers"* and 88.9% of "*moderate metabolizers"* were smear-positive. So, at the beginning of treatment patients with **AG* genotype had somewhat more frequent TB-destruction and disintegration processes in the lungs than in **AA* genotype carriers.

At the end of in-patient treatment, destruction processes remained in 22% of the patients regardless of the *CYP3A4*1B* genotype (see Table 3). In both groups, as a result of in-patient treatment, there was a reduction of the number of patients with TB-destruction, for example, in carriers of the **AA* genotype – by 50% ($p<0.05$; $\chi^2=11.17$) and in 60% of **AG* genotype carriers ($p>0.05$). The cessation of TB-destruction processes in **AA* genotype carriers took on average about 58 days, in carriers of the **AG* genotype – about 60 days.

Because of the in-patient treatment, the number of patients with **AA* genotype with TB-infiltration decreased by 5.8 times ($p<0.05$; $\chi^2=44.43$); with TB-dissemination – by 3.4 times ($p<0.05$; $\chi^2=21.18$). In both studied groups, as a result of in-patient treatment, TB-destruction and disintegration disappeared; declining was significant relatively to the initial level – for carriers of **AA* genotype ($\chi^2=13.94$) and **AG* genotype ($\chi^2=5.14$).

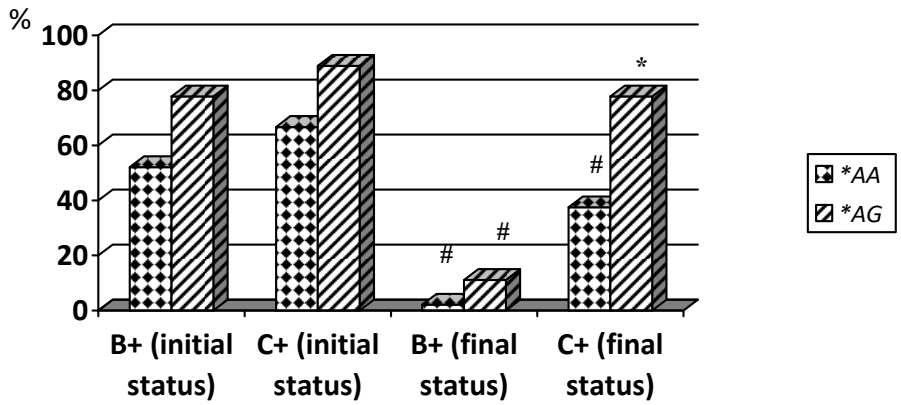
In addition, in patients with the **AA* genotype, TB-dissemination of pulmonary tissue decreased 3.4 times ($p<0.05$; $\chi^2=15.28$). At the end of in-patient treatment, the process of dissemination of pulmonary tissue was observed almost three times more often in **AG* genotype carriers than in **AA* carriers ($p<0.05$; $\chi^2=4.67$). At the same time, the resorption of TB-lesions in the lung tissue was observed in 81.2% of **AA* genotype carriers and in 66.7% of **AG* carriers ($p<0.05$; $\chi^2=131.37$ and $\chi^2=9.00$ compared to the initial level).

According to microscopy data, at the time of discharge from the hospital 97.9% of **AA* genotype carriers and in 88.9% of **AG* genotype carriers were smear-negative. At the same time, the cessation of bacterial discharge occurred in 96.0% of TB-patients with the **AA* genotype ($p<0.05$; $\chi^2=60.76$) and in 83.7% with the **AG* genotype ($p<0.05$; $\chi^2=8.1$). At the same time, the conversion of smear-positive into smear-negative status in both groups took 55–59 days.

Following the cultural method, at the end of in-patient treatment, smear-positive status was observed in 37.5% of **AA* genotype carriers and 77.8% of **AG* genotype carriers, means patients with the **AG* genotype were smear-positive in 2.1 times more often than carriers of the **AA* genotype ($p<0.05$; $\chi^2=5.52$). As a result of treatment, the number of smear-positive with genotype **AA* decreased by 43.7% ($p<0.05$; $\chi^2=16.36$), with genotype **AG* – only by 12.5% ($p>0.05$). The conversion of smear status took 70–71 days in both groups.

At the beginning of in-patient treatment, a slightly higher level of bilirubin, ALT, AST and GGT activity was observed in **AA* genotype carriers than in **AG* genotype carriers ($p>0.05$) (Table 4).

After completion of the in-patient treatment, carriers of the **AA* genotype had a 12.6% decreasing of total bilirubin in the blood ($p=0.040$; CI=0.07...3.35), while in **AG* genotype carriers it insignificantly decreased by 24.7% ($p>0.05$) (see Table 4). Also, the number of patients with hyperbilirubinemia among carriers of the **AA* and **AG* genotype decreased from 31.0% to 11.7% ($p<0.05$; $\chi^2=4.75$) and from 28.6% to 14.3% ($p>0.05$) respectively. At the end



* – $p<0.05$ (relatively to the patients with **AA* genotype)

– $p<0.05$ (relatively to the initial level of correspondent group)

Fig. 2. Frequency of smear-positive status according to bacterioscopy (B+) or cultural (C+) method and regarding to *CYP3A4*1G* polymorphism at the beginning (initial status) and at the end (final status) of in-patient treatment

Table 4

Biochemical indexes in blood depending on *CYP3A4*1B* polymorphism (M±SEM)

	At the beginning of in-patient treatment		After in-patient treatment	
	***AA**	***AG**	***AA**	**AG*
Bilirubin (total), mM/l	15.28±0.68	15.13±2.17	13.57±0.47#	12.13±1.71
Thymol	1.98±0.11	2.50±0.48	2.08±0.11	2.24±0.49
ALT, units	23.88±1.71	17.29±3.57	25.56±1.70	14.57±3.32*
AST, units	26.63±1.03	24.57±3.56	29.11±1.18	23.86±3.27
GGT, units	32.24±2.39	27.43±4.69	33.69±1.62	25.17±2.77

Footnote: # $p<0.05$ – relatively to the initial level of correspondent group;

* $p<0.05$ – relatively to the patients with **AA* genotype

of in-patient treatment, there were slight changes in thymol test parameters in both groups. After in-patient treatment, the activity of cytolysis markers as ALT and AST, and the cholestasis marker as GGT in TB-patients with **AA* genotype increased insignificantly by 7.0%, 9.3% and 4.5% ($p>0.05$); in patients with the **AG* genotype, the activity of ALT, AST and GGT, on the contrary, had a tendency for decreasing – by 18.7%, 3.0% and 9.0% ($p>0.05$); a similar trend was observed concerning the number of patients with increased activity of ALT, AST and GGT. At the end of treatment, the average activity of ALT in carriers of the **AA* genotype was 1,8 times higher than in carriers of the **AG* genotype ($p=0.046$; CI=-0,26...22,24).

Discussion. The obtained data regarding slightly lower serum concentration of rifampicin in **AG* genotype carriers may be related to the peculiarities of the serum concentration of isoniazid, which can affect the enzymatic activity of the liver, including the CYP3A4 enzyme. Differences in the intensity of drug metabolism depending on the *CYP3A4*1B* genotype may also be due to the presence of a mutant allele of *CYP3A4*1B (*G),* which is associated with a twofold increase in gene promoter activity [14]. It is likely that the decreasing in CYP3A4 activity in carriers of "wild" **A* allele is due to the presence of a transcriptional suppressor. Therefore, the phenotypic effects of the mutated allele **G* may be associated with a decrease in the attachment of the transcriptional suppressor and, accordingly, greater gene expression and greater enzymatic activity of CYP3A4, which in turn causes faster metabolism of the medicines, including rifampicin [15].

A more severe condition at the beginning of treatment and a higher prevalence of cases of subeffective rifampicin concentration in carriers of the mutated allele *CYP3A4*1B (*G)* could explain worse results of the in-patient treatment. So, at the end of in-patient treatment, the process of TB-dissemination of pulmonary tissues appeared in **AG* genotype almost three times more often than in **AA* genotype carriers ($p<0.05$); resorption of TB-lesions in the lung tissues appeared in 81.2% of **AA* genotype carriers ($p<0.05$) and in 66.7% of **AG* genotype carriers ($p<0.05$).

According to the obtained results, it was established that both at the beginning and at the end of in-patient treatment, carriers of the mutated allele **G* had a lower risk of hepatotoxicity than carriers of the "wild" allele **A*. After in-patient treatment, the activity of the cytolysis indexes ALT and AST, and the cholestasis index GGT in TB-patients with **AA* genotype increased insignificantly, while in patients with the **AG* genotype, the activity of ALT, AST, and GGT, on the contrary, slighly decrease. This could be explained by a higher serum concentration of rifampicin and slightly higher serum concentration of isoniazid in patients with **AA* genotype, compared to the group of **AG* genotype carriers. At the same time, according to previous studies, according to the *CYP3A4*1G* genotype, in "*slow metabolizers"* (mutant homozygous genotype), the risk of developing of hepatotoxicity during anti-tuberculosis therapy exceeded the similar indicator of "*rapid metabolizers"* [9].

Conclusions.

1. Patients with **AG* genotype of the *CYP3A4*1B* locus two hours after administration of rifampicin had a sub-therapeutic concentration of rifampicin 5 times more often than **AA* carriers ($p<0.05$); 4 hrs after administration – by 20% more often ($p<0.05$); 6 hrs after administration – almost 10 times more often than **AA* carriers ($p<0.05$).

2. At the end of in-patient treatment, the process of tuberculous dissemination of lung tissue was observed almost three times more often in **AG* genotype carriers of the *CYP3A4*1B* locus than in **AA* carriers ($p<0.05$).

3. After in-patient treatment, the activity of cytolysis indexes as ALT and AST, and the cholestasis index as GGT in TB-patients with **AA* genotype increased insignificantly by 7.0%, 9.3%, and 4.5%, respectively ($p>0.05$); while in patients with the **AG* genotype, the activity of ALT, AST and GGT, on the contrary, had a tendency for decreasing – by 18.7%, 3.0% and 9.0%, respectively ($p>0.05$).

4. At the beginning of anti-tuberculosis chemotherapy, it is recommended to determine the *CYP3A4*1B* genotype in patients with pulmonary tuberculosis, which allow to identify the groups of patients with the **AG* genotype, which is characterized by a greater risk of developing sub-therapeutic rifampicin concentrations in the blood during treatment and prove the usefulness of personalized choice of rifampicin dosage according to the *CYP3A4*1B* genotype.

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