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CYP2E1-DEPENDENT VARIATIONS IN HEPATOCYTES DAMAGE DURING TREATMENT OF TUBERCULOSIS

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Relevance. Investigation of polymorphism in a locus of CYP2E1 as the prognostic factor of drug induced hepatotoxicity at anti-TB therapy is significant due to the influence of CYP2E1 on drug metabolism.

The objective of investigation is to analyze association of rs2070676 CYP2E1 gene polymorphism with drug-induced hepatotoxicity by means of the clinical-laboratory values of serum transaminases at anti-TB treatment.

Materials and methods. The study involved 47 patients with a drug susceptible tuberculosis first time discovered. 58 healthy volunteers comprised a control group. Laboratory indices were determined in venous blood three times: before the treatment as baseline; in 2 months of intensive therapy (isoniazid, rifampicin, ethambutol, pyrazinamide), then in 4 months of maintenance therapy (isoniazid, rifampicin). Serum activities of enzymes ALT, AST and GGT were measured by standard algorithm on automatic analyzer BS-300. Analysis of rs2070676 polymorphism of CYP2E1 gene was performed by polymerase chain reaction using standard PureLink® Genomic DNA Kit for Purification of Genomic DNA; Manufacturer of INVITROGEN (USA). For statistical processing, IBM SPSS Statistics 23 was applied.

Results. Investigation of serum ALT and AST in patients with major genotype CYP2E1 (C/C) showed the lower baseline ALT and AST levels comparing to the control group, which might be caused by suppression of hepatocytes functions at development of disease. Anti-TB treatment caused an increase in ALT and AST levels comparing to the baseline in patients with major CYP2E1 (C/C) genotype. In the group with C/G polymorphism the baseline ALT level didn't differ much from the baseline of the control group; it showed a decrease after intensive therapy and returned back to initial level at maintenance therapy. This might be related to the certain protective property of CYP2E1 gene polymorphism. The AST level was increased after intensive therapy (in smaller extend than for the patients with major C/C genotype) and remained on the same level at maintenance therapy. Study of GGT showed a gradual increase regardless of genotype.

Conclusion. According to the data of experiment the status of hepatocytes in patients with tuberculosis at baseline and during treatment was different depending on CYP2E1 genotype. The results of experiment indicate that CYP2E1 gene polymorphism has a certain protecting role. It reduces the level of drug metabolites and hepatotoxicity which cause the mitochondrial dysfunction.

Key words: transaminase, antituberculosis therapy, hepatotoxicity, mitochondrial dysfunction, polymorphism

Relevance. Tuberculosis is one of the major social problems nowadays which concerns all countries in the world including Ukraine. Modern antituberculosis treatment requires to use the long-term chemotherapy (6-20 month depending on the type and severity of disease). Despite the high efficiency, the first line medications (isoniazid, rifampicin, pyrazinamide, ethambutol) have noticeable adverse effects, the most common of which is hepatotoxicity [1, 2]. The mechanisms of drug-induced hepatotoxicity development, including isoniazid-associated, are related to the toxicity of drug metabolites [3-5] which are formed with involvement of cytochrome P-450 enzymes [6]. The risk of hepatotoxicity development depends on polymorphism of xenobiotic detoxification genes. Mononucleotide polymorphisms have an influence on the activity of cytochrome P-450 enzymes [7] which specify the pathways of drug metabolism.

The metabolic inactivation of drugs such as isoniazid and rifampicin take place in presence of enzyme CYP2E1, the component of cytochrome P 450. The polymorphism of CYP2E1 (rs2070676) gene is related to the replacement of Cytosine (C) with Guanine (G) in tenth chromosome that may change the enzyme activity. The large number of CYP2E1 gene mutations are described [], however its influence on the activity of enzyme CYP2E1 is not fully studied. This makes it important to study the polymorphism in a locus of CYP2E1 gene as a prognostic factor of drug induced hepatotoxicity at antituberculosis treatment.

The objective of the study is to analyze the association of rs2070676 CYP2E1 gene polymorphism in tuberculosis patients with drug -induced hepatotoxicity by means of the clinical-laboratory values of serum transaminases (ALT, AST, GGT) at the time of anti-TB treatment.

MATERIALS AND METHODS

The study involved 131 persons. Among them were 73 patients of a specialized anti-tuberculosis dispensary with a drug susceptible tuberculosis first time discovered. 58 healthy volunteers comprised a control group.

Examination and treatment were carried with the written mandatary consent of patient to participate in the trial (protocol № 128, 23.12.2019, bioethics commission of Bogomolets National medical university).

The patients were treated with a standard regimen during 6 months: 2 months of intensive therapy (IT – isoniazid, rifampicin, ethambutol, pyrazinamide), then 4 months of maintenance therapy (MT - isoniazid, – rifampicin). Laboratory indices were measured in venous blood three times: first time – before the treatment as baseline; second time – in 2 months of intensive therapy, third time – in 4 months of maintenance therapy. Only 47 patients were monitored in this way, others were excluded from the study for different reasons. The median age in the group of patients was 42,7 ± 2,2 year; it was comparable with the median age of the control group. The group of patients contained a larger number of men in comparison to the control group but the difference was insignificant.

Serum activities of enzymes ALT, AST and GGT were measured by standard algorithm with automatic analyzer BS-300. Analysis of rs2070676 polymorphism of CYP2E1 gene was performed by polymerase chain reaction using standard PureLink® Genomic DNA Kit for Purification of Genomic DNA; Manufacturer of INVITROGEN (USA). For statistical processing, IBM SPSS Statistics 23 was applied. The data in the groups were compared by means of univariate analysis with non-parametric Kruskal-Wallis test. The diagrams were presented with a confidence interval (95% confidence interval).

Table 1

Analysis of distribution of alleles and genes of CYP2E1 in the control group and in a group of TB patients, % (number of persons in a group)

Genetic marker/ group	Control group, n = 58	TB patients, n = 73
C/C	74% (43)	75% (55)
C/G	26% (15)	25% (18)
G/G	0	0
C	87% (101)	87,6 % (128)
G	13% (15)	12,4% (18)

RESULTS AND DISCUSSION

The first step of research was an analysis of gene CYP2E1 genotype distribution (table 1). The percentage of gene polymorphism carriers was similar in the group of TB patients and in the control group; it indicates that there is no association of CYP2E1 gene polymorphism with development of tuberculosis. Major C/C genotype was found in ¾ cases in both groups, heterozygous C/G polymorphism was found in ¼ cases. Homozygous mutation G/G was not found.

Alanine aminotransferase (ALT) is an endogenic enzyme of transferase group widely used in medical practice as the marker in laboratory diagnostics of liver damage. Investigation of serum transaminase activity showed the median value of ALT in the control group equal to 0,47 mkkat (27.6 U/l). It corresponds well to the reference value of < 41 U/l for men and < 31 U/l for women. The level of serum ALT in the group of TB patients before treatment was 0.17 mkkat, 2.5 times lower than in the control group (fig. 1A).

After treatment by the first line medications which are potentially hepatotoxic the level of serum ALT was elevated 2 times (it is commonly interpreted as inflammation) but its absolute value remained within the range of reference values (0.37 mkkat) and was still

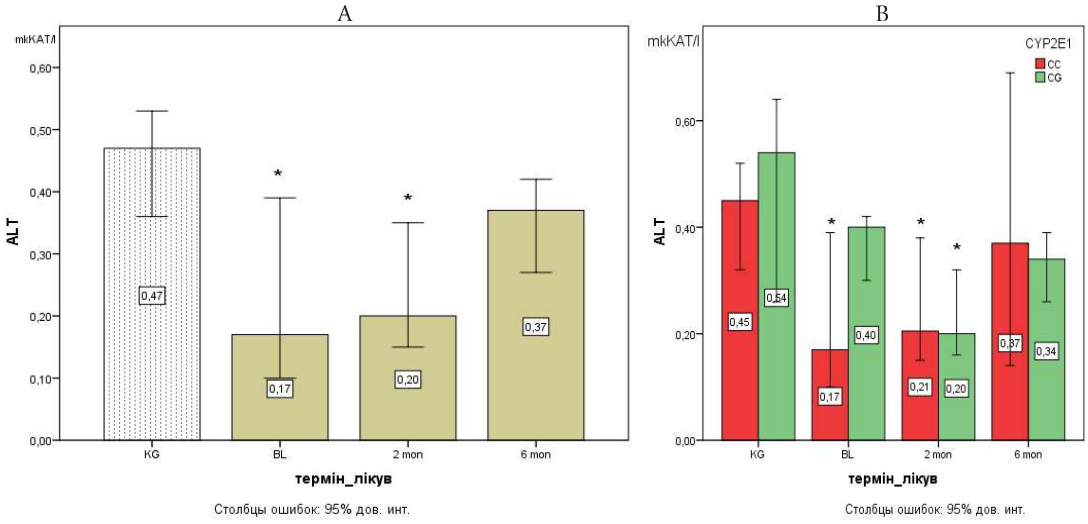

Fig. 1. Serum ALT levels in the control group and group of TB patients: baseline; in 2 months of intensive therapy; after 6 months of therapy. A – the overall group of patients; B – depending on CYP2E1 genotype. * P <0,05 compared to the corresponding category of the control group

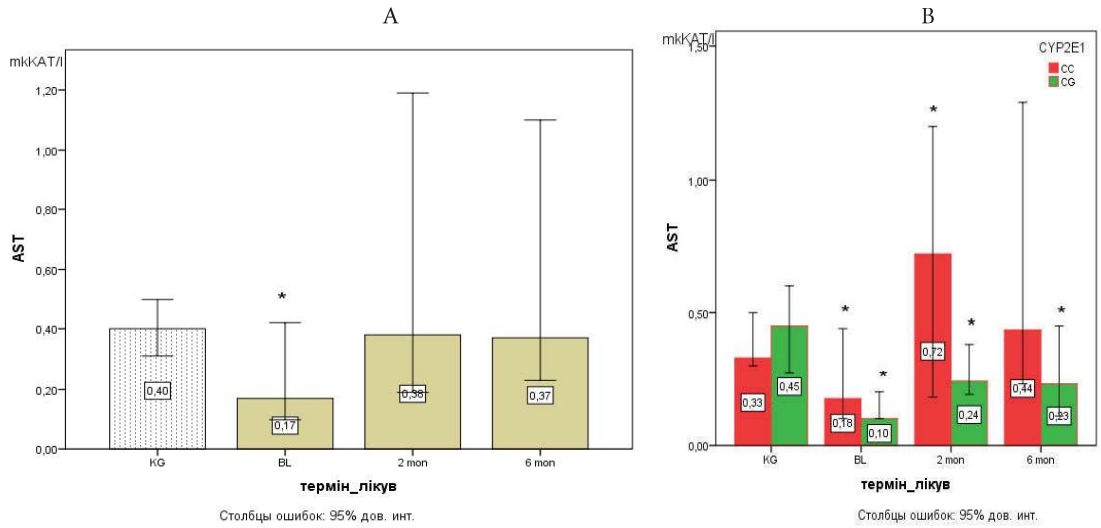

Fig. 2. Serum AST levels in the control group and group of TB patients: baseline; in 2 months of intensive therapy; after 6 months of therapy. A – the overall group of patients; B – depending on CYP2E1 genotype. * P <0,05 compared to the corresponding category of the control group

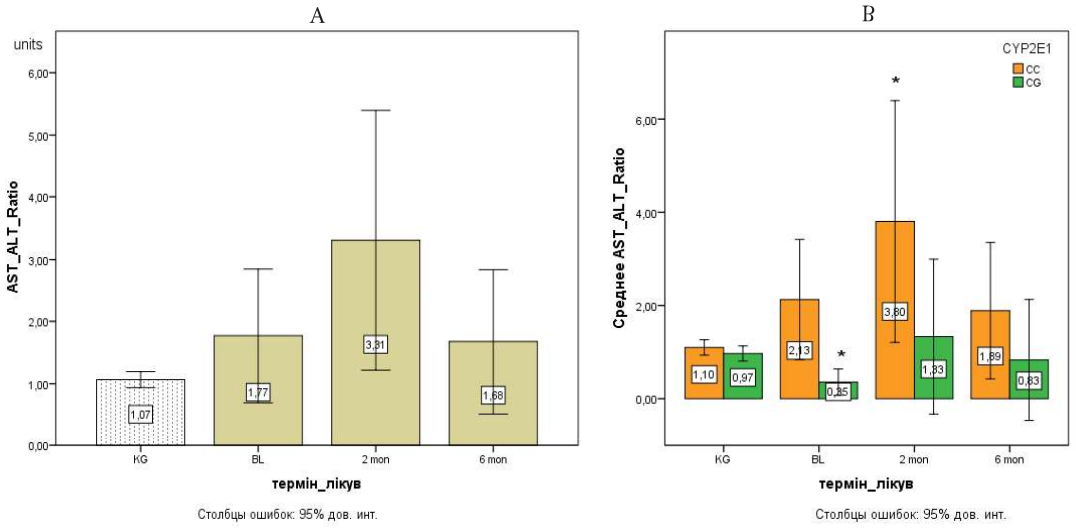

Fig. 3. De Ritis ratio (AST/ALT ratio) in the control group and group of TB patients: baseline; in 2 months of intensive therapy; after 6 months of therapy. A – the overall group of patients; B – depending on CYP2E1 genotype. * P <0,05 compared to the corresponding category of the control group

lower than in the control group of healthy volunteers. In such case the comparison of ALT levels measured for the group of TB patients with the value measured for the control group of healthy volunteers looks unreasonable because the risk of misinterpretation.

Antituberculosis treatment increased the ALT level in the group of TB patients. After 6 months of treatment (intensive and maintenance therapy) the ALT level was 2 times higher than the baseline, that indicates the development of hepatocytes inflammation. Such response to the therapy was shown only by the carriers of major C/C genotype (fig. 1B).

The level of aspartate aminotransferase (AST) is an important biochemical criteria of hepatocytes status: increased serum AST indicates the larger damage of tissue due to the larger content of mitochondrial AST in a cell. The baseline AST in the group of TB patients was much lower comparing to the control group (fig. 2A). After 2 months of intensive therapy it became 2 times higher (but still lower than in the control group); at the time of maintenance therapy it remained on the same level. Thus, comparison of level of serum AST in the group of TB patients with the control group of healthy volunteers also looks unreasonable.

The AST level of patients with major C/C genotype demonstrated large increase in the stage of intensive therapy (4 times higher than the baseline). It is typical for the mechanism of hepatotoxicity development related to the processes in mitochondria. During maintenance therapy the gradual decrease of AST was observed. In the

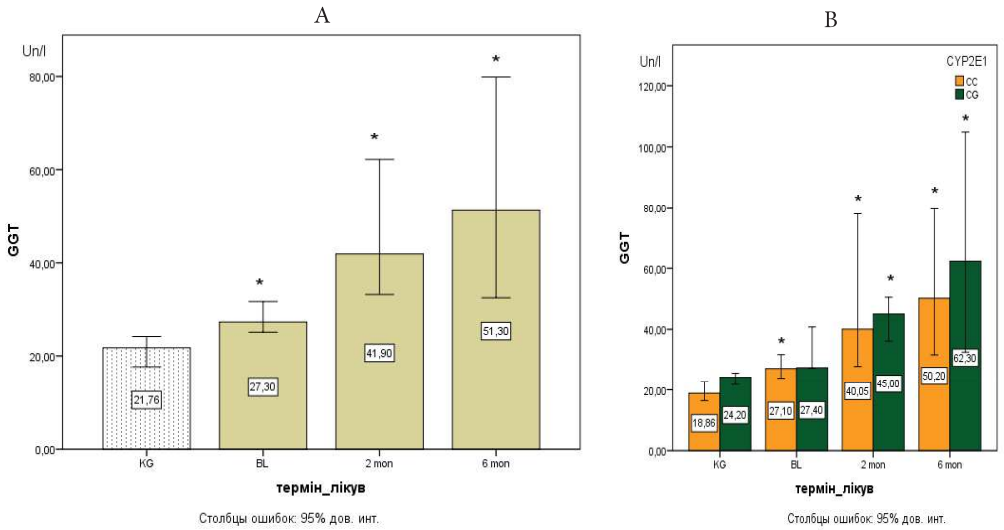

Fig. 4. Serum GGT levels in the control group and group of TB patients: baseline; in 2 months of intensive therapy; after 6 months of therapy. A – the overall group of patients; B – depending on CYP2E1 genotype. * P <0,05 compared to the corresponding category of the control group

group of carriers of C/G genotype the AST level became 2 times higher after intensive therapy; its value remained the same during maintenance therapy.

Study of De Ritis ratio in the group of TB patients showed its increase almost 2 times after intensive therapy (fig. 3A). Maintenance therapy returned the ratio back to the normal value (1,33±0,42). The sharp increase of De Ritis ratio during the stage of intensive therapy is typical for the cell necrosis which cause a release of cytosolic and mitochondrial AST into the serum. Analysis of De Ritis ratio for the carriers of major C/C genotype showed an increased level before the treatment and after intensive therapy which was getting back almost to the normal level at maintenance therapy. The carriers of C/G polymorphism showed the abnormally low baseline De Ritis ratio, which is more typical for inflammation. The gradual increase of De Ritis ratio almost to the normal level was observed during treatment (fig. 3B). This demonstrates the difference in the mechanisms of liver damage depending on the genotype and indicates the certain protecting role of CYP2E1 gene polymorphism.

Gamma-glutamyl transferase (GGT) is used as the laboratory marker of drug intoxication. The baseline GGT in the group of TB patients was a slightly higher than in the control group (fig. 4A). Anti-TB treatment caused the graduate increase of enzyme activity. After completing the treatment, the level of GGT was 2 times higher than the baseline. Genotype didn't affect the overall tendency, the elevation of GGT was observed regardless to the genotype of patients (fig. 4B).

There are numerous studies considering drug-induced hepatotoxicity at anti-TB treatment however just in some of it the baseline levels of biochemical markers measured for TB patients were compared with the corresponding values of healthy persons. The large deviations of baseline ALT in patients (without co-diseases) were not observed [9, 10] or it was reported the moderate increase of ALT associated with the larger risk of hepatotoxicity development [11]. An exception is the study [12], where it was mentioned a low baseline ALT (7.5±3.5 U/l) which corresponds well with our data.

The factors affecting ALT and AST levels are age [13] and gender. In our study the median age and gender distributions in the group of TB patients were comparable with those in the control group. Transaminase level also correlates with the body mass index (BMI) and lean mass index (LMS) [14, 15], the larger BMI is associated with larger ALT and AST. It was also reported that elevated ALT can be associated with alterations in glucose and lipid metabolism: reduced insulin sensitivity and glucose tolerance, increased fatty acids and triglycerides content [16]. Since in this study the BMI of TB patients was not taken into consideration, we cannot estimate its effect on baseline ALT level.

The low baseline level of transaminases in the group of TB patients might be related to the changes in fatty acid profile of hepatocyte membrane caused by development of tuberculosis. In detailed review [17] it was generalized that development of tuberculosis is accompanied by disorders of lipid metabolism: increased LDL, decreased HDL, changed ratio of free to esterified cholesterol. Similar observations were made by the authors of [18] which noted decreased free cholesterol, HDL, albumin and free fatty acids in TB patients. Disorders of lipid metabolism, its influence on the composition of lipoproteins and phospholipid profile of cell membranes worth the further study because the previous were mostly focused on the other aspects of the problem: on investigation of metabolism, transport and functions of lipids in mycobacteria cell wall, on the mechanisms of cholesterol and fatty acid utilization [19, 20].

We suppose that the low baseline level of ALT and AST observed in the group of TB patients might be explained by suppression of hepatocyte functions at disorder of lipid metabolism, although this question requires further study.

According to the results of experiment the carriers of C/G polymorphism had higher baseline ALT which didn't differ much from ALT level of the control group. Intensive therapy reduced the enzyme activity 2 times; maintenance therapy returned it at initial level. It might indicate that CYP2E1 heterozygous mutation provides the lower hepatocytes damage and associates with better regenerative ability.

The AST level of the carriers of major genotype was sharply increased after therapy that shows the high response of hepatocytes to the toxicity of first-line antituberculosis drugs. The carriers of C/G polymorphism demonstrated the smaller increase of AST comparing to the carriers of major allele. It might be assumed that the small variations of transaminase levels indicate the less intensive damage of mitochondria in the cell. The presence of gene polymorphism can be regarded as a protecting factor which provides the less intensive development of mitochondrial dysfunction.

Thus, the low baseline level of ALT in TB patients might be caused by suppression of hepatocyte functions at disorder of lipid metabolism. The use of transaminase values measured for healthy volunteers as baseline may mask the manifestation of hepatotoxicity development in TB patients. The mechanisms of hepatocytes damage before the treatment and during therapy were different depending on the gene CYP2E1 genotype. The heterozygous mutation contributed to the smaller hepatocytes damage at anti-TB treatment.

CONCLUSIONS

Distribution of gene CYP2E1 polymorphism in the group of healthy volunteers and in the group of TB patients were similar; it indicates that there is no association of CYP2E1 gene polymorphism with development of tuberculosis. Every fourth person had heterozygous polymorphism C/G. Homozygous mutation G/G was not found.

According to the experimental data the risk of drug-induced hepatotoxicity development was higher among the carriers of major C/C genotype. The patients with heterozygous gene CYP2E1 C/G polymorphism had lower extend of hepatocytes damage.

CYP2E1 gene polymorphism probably carries a certain protecting role: it reduces the level of drug metabolites and hepatotoxicity which cause the mitochondrial dysfunction.

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CYP2E1-ЗАЛЕЖНІ ВІДМІННОСТІ УШКОДЖЕННЯ ГЕПАТОЦИТІВ ПІД ЧАС ЛІКУВАННЯ ТУБЕРКУЛЬОЗУ

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Актуальність. Дослідження поліморфізму локусу CYP2E1, як прогностичного фактору розвитку гепатотоксичних реакцій під час протитуберкульозної терапії є актуальним через значний вплив CYP2E1 на метаболізм лікарських засобів.

Метою дослідження був аналіз асоціації поліморфізму rs2070676 гену CYP2E1 у хворих на туберкульоз із розвитком гепатотоксичності за клініко-лабораторними показниками трансаміназ крові на фоні протитуберкульозної терапії.

Матеріали та методи. В дослідженні приймали участь 47 пацієнтів з чутливою формою туберкульозу вперше виявлені. Контрольну групу порівняння складали 58 здорових добровольців. Лабораторні показники визначали в венозній крові: до початку лікування як базовий рівень; через 2 місяця інтенсивної терапії; через 4 місяця підтримуючої терапії. Активність ферментів АЛТ, АСТ та ГГТ в сироватці крові визначали за стандартними методиками на автоматичному аналізаторі BS-300. Аналіз поліморфізму rs2070676 гена CYP2E1 проводили методом полімеразної ланцюгової реакції з використанням стандартних реактивів «PureLink® Genomic DNA Kit For Purification of Genomic DNA»; виробник INVITROGEN (США). Для статистичної обробки використовували пакет IBM SPSS Statistics 23.

Результати. Вивчення сироваткової активності ферментів АЛТ та АСТ у хворих на туберкульоз показало зниження базового рівня АЛТ та АСТ відповідно до рівня контрольної групи, що може бути пов'язано з пригніченням функцій гепатоцитів під час розвитку захворювання. У динаміці лікування пацієнтів носіїв мажорного генотипу CYP2E1 (C/C) спостерігалося збільшення активності АЛТ та АСТ відповідно до базового рівня. У носіїв поліморфізму C/G базова активність ферменту АЛТ мало відрізнялась від аналогічного показника контрольної групи та демонструвала помітне зниження в ході інтенсивної терапії і відновлення до базового рівня на стадії підтримуючої терапії, що може свідчити про певні протекторні властивості поліморфізму гену CYP2E1. Рівень активності АСТ у носіїв поліморфізму збільшувався на стадії інтенсивної терапії, але не так значно, як для

носіїв мажорного генотипу, та подалі залишався незмінним. Дослідження рівня ГГТ – показало поступове підвищення рівня ферменту незалежно від генотипу.

Висновок. За даними дослідження функціональний стан гепатоцитів у хворих на ТБ відрізнявся, як на базовому рівні, так і у відповідь на терапію, в залежності від генотипу гену CYP2E1. Поліморфізм гену CYP2E1 виконує певну протекторну роль, зменшує кількість метаболітів протитуберкульозних ліків і гепатотоксичність, яка реалізується за рахунок мітохондріальної дисфункції.

Ключові слова: трансамінази, протитуберкульозна терапія, гепатотоксичність, мітохондріальна дисфункція, поліморфізм

CYP2E1-ЗАВИСИМЫЕ ОТЛИЧИЯ ПОВРЕЖДЕНИЯ ГЕПАТОЦИТОВ ПРИ ЛЕЧЕНИИ ТУБЕРКУЛЕЗА

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Актуальность. Исследование полиморфизма локуса CYP2E1, как прогностического фактора развития гепатотоксических реакций при антитуберкулезной терапии, является актуальным вследствие значительного влияния активности CYP2E1 на метаболизм лекарственных препаратов.

Целью исследования был анализ ассоциации полиморфизма rs2070676 гена CYP2E1 у больных туберкулезом с развитием гепатотоксичности по клинико-лабораторными показателям трансаминаз крови на фоне противотуберкулезной терапии.

Материалы и методы. В исследовании принимали участие 47 пациентов с чувствительной формой туберкулеза впервые выявленные. Контрольная группа сравнения включала 58 здоровых добровольцев. Лабораторные показатели определяли в венозной крови: до начала лечения как базовый уровень, через 2 месяца интенсивной терапии, через 4 месяца после поддерживающей терапии. Активность ферментов АЛТ, АСТ и ГГТ в сыворотке крови определяли по стандартным методикам на автоматическом анализаторе BS-300. Анализ полиморфизма rs2070676 гена CYP2E1 проведен методом полимеразной цепной реакции с использованием стандартных реактивов «PureLink® Genomic DNA Kit For Purification of Genomic DNA»; производитель INVITROGEN (США). Для статистической обработки использовали пакет IBM SPSS Statistics 23.

Результаты. Изучение сывороточной активности ферментов АЛТ и АСТ у пациентов с туберкулезом показало снижение базового уровня АЛТ и АСТ по сравнению с контрольной группой, что может быть связано с угнетением функций гепатоцитов при развитии заболевания.

В процессе лечения у пациентов носителей мажорного генотипа CYP2E1 (C/C) наблюдалось увеличение активности АЛТ и АСТ сравнению с базовым уровнем на фоне антитуберкулёзной терапии. У носителей полиморфизма C/G базовая активность фермента АЛТ мало отличалась от аналогичного показателя контрольной группы; демонстрировала заметное снижение в ходе интенсивной терапии и восстановление до базового уровня на стадии поддерживающей терапии, что может указывать на определенные протекторные свойства полиморфизма гена CYP2E1. Уровень активности АСТ увеличивался на стадии интенсивной терапии, но не так сильно, как для носителей мажорного генотипа, и дальше оставался неизменным. Исследование уровня ГГТ – показало постепенное повышение уровня фермента независимо от генотипа.

Выводы. Согласно результатам исследования, функциональное состояние гепатоцитов у пациентов с туберкулезом отличалось как до начала лечения, так в ответ на терапию в зависимости от генотипа гену CYP2E1. Полиморфизм гена CYP2E1 играет определенную протекторную роль, снижает количество метаболитов противотуберкулезных лекарственных препаратов и гепатотоксичность, которая реализуется за счет митохондриальной дисфункции.

Ключевые слова: трансаминазы, противотуберкулезная терапия, гепатотоксичность, митохондриальная дисфункция, полиморфизм