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RESEARCH ARTICLE

Pharmacodynamics and Hepatoprotective Properties of Drugs Affecting Metabolic Processes in Patients with Drug-Induced Liver Injury on the Background of Specific Antituberculosis Therapy

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Abstract: Objective. Data on pharmacodynamics and hepatoprotective properties of taurine, ursodeoxycholic acid and their combinations in the treatment and prevention of drug-induced liver injury on the background of specific anti-TB therapy is presented. In the study course, a retrospective analysis of primary medical documentation of 270 patients was carried out. Materials and Methods. These patients were undergoing antituberculosis therapy in regional clinical tuberculosis hospitals during 2013-2016. Clinical studies were conducted in the regional clinical tuberculosis hospital in 2016-2018. At the clinical stages, 100 patients were examined. Results and Discussion. A retrospective analysis showed that in a real clinical practice, anti-TB therapy is canceled even with a moderate increase of the transaminase level. Temporary cancellation and correction of specific therapy led to a slowed-down x-ray dynamics and an increase in the length of hospital stay. It also helped to reduce clinical manifestations of liver injury and decreased enzyme activity in most patients for 8-14 days, though the transaminases absolute values remained above the reference values. Conclusion. Taurine intake in dose of 1000 mg/day for the pharmacological correction and prevention of drug-induced liver injury showed high drug efficacy both in monotherapy and combination with ursodeoxycholic acid. Taurine shows an immunomodulatory effect in patients with tuberculosis, with increase of CD3, CD4, CD16, immuno-regulatory index and decrease of CD8, the level of cytokines IL-4, IL-6 and TNF-α.

Keywords: *Drug-induced liver injury, Specific antituberculosis therapy, Pharmacodynamics, Hepatoprotectors, taurine, Ursodeoxycholic acid.*

Introduction

Among the exogenous toxic hepatitis causes the third most common one is drug-induced liver damage. Organ damage is caused by drugs taken for medical reasons at therapeutic doses. It is second only to liver damage caused by alcohol and its substitutes.

The literature provides conflicting information on the prevalence of drug-induced liver damage (drug-induced liver injury (DILI)), according to different authors, they range from 5.4% to 85.7% [1-3]. This is due to the fact that in the majority of drug-related liver diseases initially proceed mildly and do not require hospitalization.

Through, it cannot be ruled out, that a large proportion of hepatitis and cirrhosis, regarded as cryptogenic, are in fact associated with a medicinal lesion. The overall mortality rate for drug-induced liver damage is about 5-11.9% [4]. Anti-tuberculosis and antibacterial agents are in the first place as a factor causing liver damage.

The most common hepatotoxic effects are drugs used for specific anti-TB chemotherapy [4-6]. According to World Health Organization (2018), there are more than twenty million tuberculosis patients in the

world, so the extent of the problem is easy to assess.

Depending on the morphologic changes determined on liver biopsy, several various drug-induced lesions are noted, as follows: necrosis of hepatocytes from I and III acinus zones, mitochondrial cytopathies, drug-induced hepatic fibrosis. Among vessels pathologies we noted: liver vessels lesions (hepatic venules obstruction, aneurysm-shaped sinusoidal dilatation, venous thrombosis and obliteration), acute or chronic medication-induced hepatitis.

Also, biliary system changes included tubular, tubular-parenchymal and intraductal cholestasis, drug-induced biliary sludge (cholesterin stone, pigment stones and calcium salt accumulation in biliary system and gallbladder), drug-induced sclerosing cholangitis. As a possible outcome we note drug-induced hepatic tumors [3, 5, 7]. Despite the successful antituberculous therapy the common side effects are narrowing the CT conduction and make one of the causes of its efficiency failure [6].

This is connected with the fact, that beside of treatment regimen change there's a need to reduce the most anti-TB efficient drugs. Mutually aggravating effects of TB and liver pathology and the long-term use of antituberculosis therapy create conditions for medical complications in the treatment process [3]. In this regard, the problem of prevention and treatment of liver medicinal lesions is an extremely essential component of disease therapy. Clinical and laboratory features and pathogenetic mechanisms of liver damage in exogenous toxic hepatitis still aren't understood well.

As considered, nonspecific changes occur at the crucial pathogenesis stages due to the common metabolic processes and oxidative stress and the development of cellular damage [8-11]. Therefore, it seems relevant to optimize their pathogenetic correction with drugs that affect metabolic processes with antioxidant and antihypoxant properties [12, 13].

Currently used hepatoprotectors are often not effective enough and can contribute to the growth of cholestasis and enzymatic hyperactivity of the liver cells [4]. The exact mechanisms of these drugs have been studied insufficiently, and, in most cases their influence are only predicted, which makes it difficult to determine the indications for their use [14]. All this dictates the need for a targeted search for new measures and means to protect the liver and effectively treat its lesions.

As reported recently, taurine (2-aminoethanesulfonic acid) helps to improve energy and metabolic processes, normalize cell membrane function, stimulates reparative processes in various diseases [15-20]. It is noted, that taurine has a therapeutic potential for acute acetaminophen-induced liver damage [21]. In a number of studies of the antituberculosis therapy side effects a decrease in the taurine level is noted [22, 23].

Experimental use of taurine against the background of antituberculosis therapy in laboratory animals showed an increase of taurine concentration in plasma and leukocytes, increase of glutamic acid and reduced glutathione, a decrease in arginine concentration in plasma and its increase in leukocytes. Thus, it can be assumed that the use of taurine for TB increases the antioxidant reserves and resistance, and the total effectiveness of chemotherapy. Taurine is considered as the important modulator of many pathophysiological processes in the human body, with great therapeutic potential. However, its use for the pharmacological correction of exogenous-toxic liver damage has been yet poorly studied, which determined the relevance of our study in real clinical practice.

Currently-used hepatoprotectors are often not effective enough and can contribute to the growth of cholestasis and enzymatic hyperactivity of liver cells [4]. The exact mechanisms of action of drugs in this group have been studied insufficiently, and, in most cases, are only assumed, which makes it difficult to determine the indications for their use [14]. All this proves the need for a targeted search for new measures and means for liver protection and effective treatment of its lesions.

Thus, the purpose of this study was to optimize the pharmacotherapy of drug-induced liver lesions on the background of specific antituberculosis therapy based on the study of hepatoprotective properties and

pharmacodynamics of drugs that affect the metabolic processes: taurine and ursodeoxycholic acid (UDCA).

Materials and Methods

In the course of the study, a retrospective analysis of primary medical documentation of 270 patients undergoing antituberculosis therapy was carried out in regional clinical tuberculosis hospitals during 2013-2016. Clinical studies were conducted in the Irkutsk Regional Clinical Tuberculosis Hospital in 2016-2018. At the clinical stages, 100 patients were examined. This study has been approved by the Regional Independent Ethics Committee.

All subjects signed the Informed Consent Form prior to inclusion in the study. The study was conducted in accordance with the principles of the Helsinki Declaration of the International Medical Association, adopted in 1996, and recommendations on the ethics of biomedical research. Compliance with the requirements of bioethics is confirmed by the results of the examination of the Regional Ethics Committee. All study protocols were examined and approved by the ethical committee.

Inclusion criteria: the presence of confirmed diagnosis of pulmonary tuberculosis, voluntary signed informed consent; age over 18 years; ability to comply with prescriptions. Exclusion criteria: viral hepatitis; HIV; pregnancy and lactating; surgery, infection for last 8 weeks; clinically significant disease.

All patients were examined upon admission, then monthly until the end of the course of treatment, more often if needed. The examination included a record of complaints, anamnesis and examination. All patients underwent clinical and biochemical blood tests, blood tests for markers of syphilis, HIV infection, viral hepatitis, coagulogram, blood group, Rh factor for treatment standards. Additionally, the indicators of immune status were studied: the number of T-lymphocytes (CD3, CD4, CD8, CD16, immunoregulatory index) and cytokine profile (TNF-α, IL-4, IL-6).

All patients underwent thorax X-ray, electrocardiography, abdominal USI with the determination of the size of the right and left liver lobes, their structure and echogenicity, diameter of portal and splenic veins, spleen area, common bile diameter, gallbladder volume, the size of the pancreatic gland and kidneys. Liver biopsy was performed according to the indications. The results of the clinical examination were recorded in individual patient registration card.

The diagnosis of drug-induced liver damage was established in accordance with the Guidelines in the Recognition and Clinical Practice Guidelines 2001 and in accordance with the consensus criteria of the Council of International Scientific Medical Institutions (CIOMS) with an increase in serum ALT (alanine aminotransferase) twice the normal value with the absence of alternative diagnoses. Roussel Uclaf Causality Assessment Method (RUCAM) was used to assess the likelihood of the association of liver damage with antituberculosis drugs.

TNF-α (Tumor necrosis factor-α) and IL-4 (Interleukin - 4), IL-10 (Interleukin - 10) levels in serum were determined with enzyme-linked immunosorbent assay (ZAO Vector-Best, RF). Uniplan spectrophotometer and incubator shaker (Elmi, Latvia) were used.

Circulating lymphocytes phenotyping was performed with flow cytofluorometry and a standard panel of antibodies to membrane antigens (CD3, CD4, CD8 and CD16 labeled with fluorochromes FITC, PE (FACS Count Reagent Kit, USA)) using a FACS Coupto cytometer (Becton Dickinson, USA). A pharmacoeconomic analysis of treatment effectiveness was conducted with cost-effectiveness method (CEA - cost-effectiveness analysis). Course therapy cost and bed/day inpatient treatment were taken into account in rubles at the official rates of 2018.

Statistical processing of the results was performed using the standard package of computer applications MS Excel - 2016 and SPSS 10.0, "Biostat, Version 4.03 by Stanton A. Glantz", "Statistica 6.0 for Windows". The threshold value of the significance of differences in bilateral tests was taken as 0.05.

Results and Discussion

The Results of Pharmacoepidemiological Studies by Retrospective Analysis Method of

Primary Documentation of Patients with Pulmonary Tuberculosis

Case histories of 175 men (65%) and 95 women (35%), age range 22-57, with tuberculosis diagnosed, were analyzed. The average age of patients (M±σ) was 35.5±21.6 years. According to the primary medical documentation, depending on the form of the process and the sensitivity of Mycobacterium tuberculosis to antibacterial drugs, they received treatment according to standard chemotherapy regimens: 1st – 117 people, 2a – 16, 2b – 56, 3rd – 64, 4th –17 people (1st mode-newly diagnosed patients with bacterial excretion and/or widespread or complicated damage of various organs; 2a mode - repeated chemotherapy after a break in treatment or for relapse with a low risk of drug resistance to mycobacterium tuberculosis; 2b treatment - patients with a high risk of drug resistance of mycobacteria; third mode - new cases-negative, with small and complicated forms of tuberculosis; 4th mode - patients with mycobacterial isolation, resistant to isoniazid and rifampicin). Patients with newly diagnosed pulmonary tuberculosis prevailed 244 (90.4%) who had not previously received antituberculosis drugs. Mild disease severity was noted in 89 (33%) patients, moderate in 104 (39%), and severe in 77 (28%).

Before chemotherapy initiation in patients with tuberculosis, biochemical parameters were recorded within reference intervals, but higher than in healthy individuals. Against the background of specific therapy, only transaminase levels were significantly changed: aspartate aminotransferase (AspAT) increased 2.43 times, alanine aminotransferase (ALAT) 2.58 times. Increased levels of transaminases by the third month of the active phase of treatment of tuberculosis were detected in 181 patients, which amounted to 67.03%. Drug-induced liver damage was diagnosed in 76 patients, which accounted for 28.1% of all patients with tuberculosis.

Among these cases, 34 women were observed with liver damage (35.78% of all women with tuberculosis, observed at the first stage) and 39 men (22.29%, respectively). As it follows, DILI incidence in women was statistically significant, 1.61 times higher than in men ($\chi 2 = 6.12$, $p = 0.0134$).

An assessment was made of the effect of age on the incidence of liver damage separately for women and men. It was revealed that already at the age of 41 years and older, patients on the background of antituberculosis therapy showed a tendency to increase the frequency of liver damage, and statistically significantly more often drug-induced liver damage developed in people over 50 years old ($\chi 2 = 14.812$, $p = 0.0001$).

This study examined the effect of the TB clinical course severity on the risk of developing liver damage. So, DILI was diagnosed in 4 patients with mild TB (4.49% of all patients with an appropriate degree of tuberculosis), 25 (24.03%) with moderate and 47 (61.03%) with severe. Thus, DILI developed significantly more frequently in patients with a high degree of disease severity ($\chi 2 = 65.603$, $p < 0.0001$).

Data analysis of the relationship of clinical forms of pulmonary TB with the frequency of DILI development are presented in Table 1.

Table 1: Connection between DILI and TB clinical forms (n = 76)

TB clinical forms	**Infiltrative n (%)**	**Disseminated n (%)**	**Total n (%)**	**Credibility**
	35 (46,05%)	**41 (53,95%)**	**76 (100%)**	**□2=33,849, p<0,0001**
Destructive changes				
with decay	28 (36,84%)	33 (43,42%)	61 (80,26%)	□2=25,086, p<0,0001
without decay	6 (7,89%)	9 (11,84%)	15 (19,74%)	□2=8,331, p=0,0048
Bacterial excretion				
MBT+	42 (55,26%)	24 (44,74%)	66 (86,84%)	□2=10,696, p=0,001
MBT –	3 (3,95%)	6 (7,89%)	9 (13,16%)	□2=2,785, p=0,076

The Table shows that DILI developed significantly more frequently in patients with disseminated form of tuberculosis with lung tissue decay and bacterial excretion ($p < 0.001$).Regardless of the regimen of antituberculosis therapy, women experienced a more pronounced increase in ALAT level in the first month of therapy — by 62%, while in men the rise was 31% from the initial level. The level of AspAT in women increased by 29.7%, in men - by 20.8%. Thymol test also increased: in women - by 23.4%, in men - by 13.5%.

In order to study the significance of biochemical parameters dynamics, a regression model was used, thanks to which ALAT and AspAT were established to reflect the cytolytic changes of hepatocytes already in the first two months from the start of therapy, regardless of the regimen used. Thymol samples are not informative, total bilirubin rises as much as possible to the fifth, alkaline phosphatase to the fourth month, but their dynamics is not statistically significant.

Thus, only ALAT and AspAT indicators can be used for laboratory control of the effect of antituberculosis chemotherapy on the state of the liver in the dynamics of routine biochemical tests with satisfactory accuracy, which reflect the development of hepatotoxic reactions before the other ones.

Analysis of the liver damage clinical manifestations showed, that they were statistically more often asymptomatic ($\chi 2 = 35.90$, $p < 0.0001$) - in 23 (30.26%) patients. Dyspeptic syndrome was detected in 12 patients (15.79%), astenic vegetative in 11 (14.47%), hepatomegaly in 14 (18.42%), a combination of syndromes was observed in 16 patients (21.05%).

There were no statistically significant differences found in the DILI development depending on the chemotherapy regimen. However, they had influence on the liver damage type. Based on the laboratory studies results, considering the ALAT, alkaline phosphatase (ALP) levels and their ratio (R coefficient), three types of liver medicinal lesions are distinguished [26]. In our study, cytolytic hepatocellular type prevailed in the 1st, 2nd and 3rd modes (ALAT> 2N, ALP = N, ALAT/ALP> 5N), with 2b - mixed (ALAT> 2N, ALP> 2N, ALAT/ALP – 2–5N), 4th — cholestatic (ALAT = N, ALP> 2N, ALAT/ALP <2N).

A retrospective analysis showed, that in a real clinic, antituberculosis therapy is reduced even with a moderate excess of transaminase level upper limit. Although DILI was diagnosed in 76 (28.1%) patients, chemotherapy was interrupted in all 181 (67.03%) patients with elevated transaminase levels ($\chi 2 = 84.905$, $p < 0.0001$). Temporary reduction and correction of specific therapy led to a slowed-down x-ray dynamics and an increase in length of hospital stay (253.9±17.8 days and 202.5±16.3, respectively ($t = 2.26$, $p < 0.048$).

Cancellation of specific antituberculosis therapy reduced the clinical manifestations of liver damage and decreased enzyme activity in most patients for 8–14 days (61 patients, 80.26%) ($\chi 2 = 88.54$, $p < 0.0001$), but absolute transaminase values remained higher than reference values. Reappointment of antituberculosis effective drugs without hepatoprotection in 69 patients (90.79%) led to the re-development of hepatotoxic reactions ($\chi 2 = 79.303$, $p < 0.0001$).

Open, Randomized, Controlled, Prospective Clinical Trial of Taurine and UDCA Pharmacodynamics and Hepatoprotective Properties in the Treatment of DILI in Patients with Tuberculosis

Patients received treatment according to the 1st chemotherapy regimen: isoniazid - 0.6 g/day; rifampicin - 0.45 g/day; ethambutol - 1.2 g/day and pyrazinamide - 1.5 g/day. At this stage of work, patients with already developed DILI on the background of specific therapy were included in the study. 100 patients with tuberculosis with DILI were randomized into four groups of 25 people.

Despite the development of DILI, we tried to preserve the intensity of chemotherapy using taurine, UDCA, their combination or milk thistle extract. The level of ALP did not change significantly ($p > 0.05$). There was a tendency to increase bilirubin ($p > 0.05$). ALAT and AspAT levels were statistically significant. Data are presented in Table 2.

Table 2: Efficacy of different treatment regimens for drug-induced liver damage in patients with pulmonary tuberculosis

Group Ia (antituberculosis therapy + taurine) (n = 25)		
	AspAT (M□m)	ALAT (M□m)
Before treatment	115,4□16,9	123,1□18,4
After treatment	44,2□6,6	45,1□6,9
Credibility	t=3,51, p<0,01	t=3,74, p<0,02
Group IIa (antituberculosis therapy + taurine + UDCA) (n = 25)		
Before treatment	115,4□16,5	124,6□13,4
After treatment	36,6□7,6	37,2□8,5
Credibility	t=4,76, p<0,001	t=5,37, p<0,001
Group IIIa (antituberculosis therapy + UDCA) (n = 25)		
Before treatment	113,5□17,9	113,5□15,7
After treatment	47,6□6,7	49,6□6,5
Credibility	t=3,06, p<0,01	t=4,09, p<0,01
Group IVa (antituberculosis therapy + milk thistle extract) (n = 25)		
Before treatment	111,7□17,4	119,5□16,7
After treatment	58,9□7,8	63,7□12,3
Credibility	t=2,05, p>0,05	t=2,05, p>0,05

The table shows that during treatment in Group IIa, liver state was normalized and ALAT and AspAT levels significantly reduced to normal values ($p < 0.001$), therapy was maintained in 24 (96%) patients of this group ($\chi2 = 1.026$, $p = 0.311$).

In Group Ia, a significant decrease in transaminases level was observed ($p < 0.01$), but the indices remained above normal and 4 (16%) patients had forced reduction of anti-TB drugs ($\chi2 = 3.243$, $p = 0.0717$). In Group IIIa, transaminases level significantly decreased ($p < 0.01$), but remained above normal in 22 patients (88%). In 5 patients (25%) their further increase was observed, which led to chemotherapy reduction ($\chi2 = 3.63$, $p = 0.05$). In Group IVa, a statistically insignificant decrease in enzymes level was observed ($p > 0.05$), antituberculosis therapy was reduced in 77% of patients ($\chi2 = 23.0$, $p = 0.0001$).

In patients with DILI-tuberculosis, dyslipidemia was observed with elevated cholesterol -5.9±0.1 mmol/l, low-density lipoprotein (LDL) - 4.55±0.27 mmol/l, reduced levels of high-density lipoprotein (HDL)-1.04±0.06 mmol/l. In the treatment of liver damage with taurine and UDCA, in Group IIa, triglycerides decreased to 1.35±0.08, cholesterol to 5.3±0.07, LDL to 3.98±0.31, HDL increased to 1.24±0.06. Groups IIIa and IVa showed no significant changes in these indicators ($p > 0.05$).

Blood coagulation disorders were detected in tuberculosis patients with liver damage: a decrease in the prothrombin index (92.4±2.6%), an increase in aPTT (activated partial thromboplastin time) (43.7±2.4 sec). Three months later, against the background of taurine and UDCA, a reliable normalization of the prothrombin index (96.6±2.3%), INR (International normalized ratio) (1.1±0.03), aPTT (36.4±2.2 sec) was observed ($p < 0.05$). Monotherapy with taurine, UDCA or milk thistle extract reduced coagulation disorders severity, but dynamics was not reliable ($p > 0.05$).

Thus, hepatoprotectors effectively stopped dyspeptic, asthenic vegetative syndromes and hepatomegaly. The combination of taurine and UDCA was the most effective, reliably relieving clinical syndromes of DILI faster than with Group IVa: dyspeptic for 1.3 days, asthenic vegetative for 2.4 days, hepatomegaly for 1.6 days and reduced inpatient treatment by 20.4 days. The use of taurine and UDCA in DILI treatment in patients with tuberculosis that arose against the background of specific therapy allowed to significantly reduce the frequency of chemotherapy reduction in Group Ia up to 4 patients (16%) ($\chi2 = 3.243$, $p = 0.0717$), in

Group IIa to 1 (4%) ($\chi 2 = 1.026$, $p = 0.311$), in Group IIIa up to 5 (25%) ($\chi 2 = 4.44$, $p = 0.035$), compared with group IVa - 19 (77%) ($p < 0,05$).

Against the background of complex therapy, an earlier closure of the destruction cavities was observed. In 76% of patients in Group IIa, the cavities of destruction were no longer determined by the end of the third month. In Group IVa it took place in only 44% by the end of the third month respectively ($\chi 2 = 3.75$, $p = 0, 05$).

In addition, complex sputum negativity was observed against the background of complex therapy: by the end of the first month - in 21% and 26% of Group Ia and IIa, respectively, of the second month - in 36% and 46%, by the end of the third month - in 72% and 83%. In group IV - in 14%, 26% and 54%, respectively ($\chi 2 = 3.956$, $p = 0.0467$).

In patients with DILI tuberculosis, leukopenia was observed (4.71±0.46x109/l), which is statistically significantly lower than in patients without liver damage (6.55±0.37x109/l) ($t = 3.11$, $p < 0.01$) and compared with healthy individuals (7.26±0.31 x109/l) ($t = 4.59$, $p < 0.01$). A weak T-cell proliferative response and a lack of cellular immunity were observed. The severity of immune disorders depended on liver biochemical activity.

Maximum statistically significant immunomodulatory effect was observed in Group IIa: a decrease in CD8 number was 10.45%, an increase in CD3 - 7.57%, CD4 - 10.99%, CD16 - 29.59%, immuno-regulatory index - 24.36%. Against the background of monotherapy with taurine and UDCA, positive but unreliable dynamics were observed. In group IVa, against the background of treatment, deficiency of immunity cellular level remained.

As known from the literature, tuberculosis is an interleukin-dependent immunodeficiency disease with an imbalance of regulatory subpopulations of T-lymphocytes and changes in the level of cytokines[8]. With DILI, the sensitivity of its tissue increases to the aggressive effects of reactive oxygen species and pro-inflammatory cytokines[3]. In patients with DILI, we detected a statistically significant increase in the synthesis of IL-4, IL-6 and TNF-α compared with healthy individuals ($p < 0.001$) and patients with tuberculosis without liver damage ($p < 0.01$).

A significant dependence of cytokine level on the severity of the biochemical activity of the liver during its drug-induced lesion ($p < 0.01$) was noted. With DILI therapy, cytokine levels in all groups got decreased. However, in the monotherapy groups with taurine, UDCA, changes in the cytokine profile were not statistically significant ($p > 0.05$).

In group IVa, on the background of milk thistle fruit extract, minimal dynamics of cytokines was observed, which determined its low clinical efficacy. The maximum effect with statistically significant dynamics was observed in group IIa against the background of a combination of taurine and UDCA: a decrease in the concentration of IL-4 was 30.15%, IL-6 - 36.41% and TNF-α - 48.19% ($p < 0, 05$).

Open, Randomized, Controlled, Prospective Clinical Trial of Taurine and UDCA Hepatoprotective Properties and Pharmacodynamics for the Prevention of DILI with Tuberculosis

100 patients with newly diagnosed pulmonary tuberculosis who had not previously received anti-TB drugs were examined, among them 62 men (62.0%) and 38 women (38.0%) aged 22 to 60 years (mean age 36.5±20 , 7). In the intensive care phase, chemotherapy was prescribed according to the 1st standard regimen: isoniazid - 0.6 g/day; rifampicin - 0.45 g/day; ethambutol - 1.2 g/day and pyrazinamide - 1.5 g/day for three months.

The patients were randomized into four groups of 25 people each: the Group Ib received additional taurine 500 mg 2 times a day for 3 months. Group IIb - a combination of taurine 500 mg 2 times a day and UDCA 250 mg 2 times a day for 3 months. Group IIIb received UDCA 250 mg 2 times a day for 3 months. Group IVb did not receive hepatoprotective agents.

Only ALAT and AspAT levels were subject to statistically significant dynamics. The data presented in Table 3.

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Table 3: Efficacy of various prevention regimens for drug-induced liver damage in patients with tuberculosis

Group Ib (antituberculosis therapy + taurine) (n = 25)		
	AspAT (M□m)	ALAT (M□m)
Before treatment	26,1□1,4	27,2□1,8
After treatment	20,5□1,6	23,5□1,7
Credibility	t=2,65, p<0,05	t=2,53, p<0,05
Group IIb (antituberculosis therapy + taurine + UDCA) (n = 25)		
Before treatment	26,2□1,7	27,4□2,1
After treatment	17,8□1,9	19,3□1,9
Credibility	t=2,74, p<0,01	t=3,04, p<0,01
Group IIIb (antituberculosis therapy + UDCA) (n = 25)		
Before treatment	26,2□1,8	26,8□1,9
After treatment	22,9□1,6	24,9□1,8
Credibility	t=1,07, p>0,05	t=0,72, p>0,05
Group IVb (antituberculosis therapy) (n = 25)		
Before treatment	25,1□2,1	27,2□3,1
After treatment	67,1□4,7	72,5□5,2
Credibility	t=8,34, p<0,001	t=8,14, p<0,001

From the second week of chemotherapy in Group IVb without hepatoprotection, there was a tendency to bilirubin concentration increase, however, the changes were unreliable (p> 0.05). The level of alkaline phosphatase remained within the normal range during the entire observation period in all groups (p> 0.05).

In Group IVb, significant increase in ALAT and AspAT levels was detected (p <0.001). In the prophylaxis groups receiving taurine, UDCA or their combination DILI was prevented: ALAT and AspAT levels remained within the normal range. UDCA use stabilized them in 20 patients (80%), in 3 patients (12%) there was a moderate excess of the limits of the norm and in 2 patients (8%) significant. During therapy with taurine and its combination with UDCA, the transaminases' levels were significantly reduced (p <0.05 and p <0.01, respectively).

Group IVb showed an increase in the level of transaminases in 17 patients (68%) without hepatoprotection, on the background of specific therapy; 7 of them (28%) registered the development of liver damage. In the UDCA group, anti-TB therapy was canceled in 3 patients (12%) ($\chi 2 = 32.727$, p <0.0001). The use of taurine and its combination with UDCA made it possible to preserve antituberculosis therapy in all patients of the Groups Ib and IIb ($\chi 2 = 40.0$; p <0.0001). The prophylactic administration of taurine and/or UDCA increased the clinical efficacy of chemotherapy: after three months, 92% of patients in group IIb showed positive x-ray dynamics, in group IVb without hepatoprotectors 53% ($\chi 2 = 6.144$, p= 0.0133). In addition, an earlier negative sputum test was observed: by the end of the first month - in 24% and 32% of patients in Groups Ib and IIb groups, in the second month - in 44% and 53%, by the end of the third month - in 84% and 92%; in Group IVb - in 14%, 36% and 63%, respectively.

In tuberculosis, lipid metabolism disorders were revealed as not statistically significant (p> 0.05). In the dynamics, a decrease in the triglycerides level was observed - from 1.54±0.08 to 1.18±0.07 mmol/l, cholesterol - from 5.5±0.12 to 5.1±0.13 mmol/l and LDL - from 4.21±0.37 to 3.01±0.32 mmol/l. HDL got increased from 1.13±0.08 to 1.45±0.07 mmol/l.

Though, these changes were significant only in the groups that took taurine (p <0.05). Against the background of UDCA, lipid profile was noted with stabilization. In Group IV, lipid metabolism imbalance increased during treatment.

Triglyceride concentrations significantly increased to 1.54±0.08 mmol/l and cholesterol to 5.9±0.1 mmol/l ($p < 0.05$), besides LDL (4.5±0.28 mmol/L) and cholesterol (5.9±0.1 mmol/L) exceeded the upper limit of normal.

In terms of coagulogram indices, prior to the treatment, differences in tuberculosis patients from healthy individuals were observed only in terms of aPTT (34.5±1.5 sec and 29.9±1.2 sec respectively, $t = 2.56$, $p < 0.05$). After three months of chemotherapy without hepatoprotection, negative INR dynamics was observed - from 1.03±0.05 to 1.25±0.04 ($t = 2.19$, $p < 0.05$) and aPTT - from 35.8±1, 2 seconds to 41.3±1.4 seconds, ($t = 2.32$, $p < 0.05$). Coagulopathy was detected in 6 patients with liver damage (30%). The use of taurine and UDCA helped to prevent disorders in the blood coagulation system.

In patients with tuberculosis before the onset of specific treatment, severe T-lymphocytopenia was observed in 58% of patients, CD4 decrease in 70%, a moderate CD8 increase in 51%, CD16 decrease in 56% of cases and CD4/CD8 immuno-regulatory index - in 62% patients with tuberculosis. The initial T-helper CD4 and NK-cells of CD16 effectors number in patients with tuberculosis is statistically significantly lower, and cytotoxic CD8 lymphocytes levels are higher than in healthy individuals ($p < 0.05$). The data is presented in Table 4.

Table 4: Dynamics of T-lymphocyte level in patients with tuberculosis (n = 25)

Indicator	Group Ib	Group IIb	Group IIIb	Group IVb
Mature CD3 T-lymphocytes				
Before treatment:	1556,5±38,5	1536,7±36,4	1580,4±35,3	1556,7±34,7
After treatment:	1678,3±37,5*	1668,7±37,5*	1656,7±36,5	1454,6±32,6
T-helper/inductor CD4				
Before treatment:	957,4±24,5	956,3±25,3	952,5±24,6	955,4±27,8
After treatment:	1025,5±26,6*	1051,1±23,1*	996,5±24,6	854,5±25,3*
Cytotoxic T Lymphocyte Suppressors/CD8 Killers				
Before treatment:	673,2±24,5	668,5±24,7	671,3±25,2	667,4±22,5
After treatment:	556,5±26,4*	541,3±25,5*	569,7±27,5	697,5±23,5*
CD16 Natural Killer				
Before treatment:	185,6±16,7	177,7±18,4	183,4±14,5	182,4±12,4
After treatment:	220,3±11,3*	221,1±13,6*	194,5±16,5	165,4±16,4*
CD4/CD8 Immunoregulatory index				
Before treatment:	1,434±0,15	1,443±0,12	1,454±0,14	1,445±0,12
After treatment:	1,843±0,12*	1,945±0,14*	1,765±0,14	1,258±0,16*

Note: * - changes in the dynamics are significant ($p < 0.05$).

The table shows that in Group IVb without hepatoprotection, further aggravation of negative changes was observed: the CD3, CD4 and CD16 number continued to decrease, while CD8 value increased significantly. After three months of taurine intake, CD3, CD4, CD16 number increased statistically significantly, CD8 number decreased significantly compared with baseline, with the maximum effect in Group IIb. CD4 increase and CD8 T-lymphocyte count decrease led to an increase in the immunoregulatory index by 35.3% ($p < 0.05$). Also, positive dynamics of the relative number of NK cells in Group Ib was noted in 64% of patients, in Group IIB - in 73%, and in the standard therapy group - in 33% of patients. In Group IVb, standard chemotherapy disorders of immune status persist, but they are less pronounced than before treatment. However, immune disorders worsened in patients with liver damage in this group. Studies have revealed a pronounced imbalance of the cytokine profile in the serum of patients with tuberculosis, compared with healthy individuals. On DILI prophylaxis background, a significant decrease in the levels of the studied cytokines was observed in all groups, with the most significant effect in the Groups Ib and IIb. The data is presented in Table 5.

Table 5: Cytokine level dynamics in patients with tuberculosis on hepatoprotection and specific therapy background (n = 25)

Indicator	Group Ib	Group IIb	Group IIIb	Group IVb
IL-4				
Before treatment	24,6±2,1	27,1□2,3	25,8□2,4	24,9□2,6
After treatment	18,1±1,7*	16,3□2,1*	20,2□2,0	36,8□3,7*
IL-6				
Before treatment	13,7±1,2	14,2□1,3	13,8□1,1	13,3□1,1
After treatment	10,3±1,0*	8,1□1,1*	11,7□1,0	16,9□1,2*
TNF-α				
Before treatment	35,2±3,3	38,6□3,7	35,1□3,1	34,8□3,7
After treatment	22,9±2,8*	20,1□3,3*	29,3□3,0	52,7□4,9*

Note: * - changes in the dynamics are significant ($p < 0.05$).

The table shows that the use of taurine has an immunomodulatory effect with a tendency to normalize the immune status and reduce cytokines level to concentrations close to the values of healthy individuals. Against the background of UDCA intake, cytokines level decrease was also observed, but it was less pronounced and not statistically significant ($p > 0.05$). In the group without hepatoprotection, the concentration of cytokines continued to increase significantly, with maximum values in patients with liver damage ($p < 0.05$)

Conclusion

As it was found, any prophylactic hepatoprotective course increases the antituberculosis therapy effectiveness, allows maintaining its intensity in at least 80% of patients and is more economically justified comparing to DILI treatment.

Treatment efficacy maximum percentage was observed with taurine intake and its combination with UDCA (from 85% in the treatment of liver damage to 100% in prophylactic use). Taurine-UDCA combination also had the best indicators on the "cost-effectiveness" criterion, which ensured a reduction in prophylactic costs by 63% and by 42% in the treatment of DILI.In general, taurine use in a dose of 1000 mg/day for pharmacological correction and prevention of drug-induced liver injury has shown high efficacy of the drug both in monotherapy and in combination with ursodeoxycholic acid. Inclusion of taurine in the DILI treatment regimen reduces the length of hospitalization by 11.2 days with monotherapy and by 20.1 days with a combination with ursodeoxycholic acid.

Inclusion of taurine in the DILI prophylaxis regimen reduces the length of hospitalization by 14 days with monotherapy and by 22.2 days with a combination with ursodeoxycholic acid. Taurine has an immunomodulatory effect in patients with tuberculosis, increasing CD3, CD4, CD16 numbers, immuno-regulatory index and reducing CD8, IL-4, IL-6 cytokines and TNF-α levels.

Further study of the hepatotropic properties and pharmacodynamics of targeted therapies that affect metabolic processes in patients with exogenous-toxic liver damage is considered as promising in a larger sample and long-term results observation. The study of diagnostic criteria combinations (including immune imbalance and cytokine profile indicators) as early markers of severe liver damage and monitoring the effectiveness of their pharmacological correction is also considered as necessary.

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