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ABSTRACT

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THE EFFECT OF ANTIOXIDANT THERAPY ON THE CHANGES OF CLINICAL AND LABORATORY PARAMETERS IN ALCOHOL DRINKERS WITH PULMONARY TUBERCULOSIS

Objective. Determination of the effect of antioxidants on clinical and laboratory parameters in alcohol drinkers with infiltrative newly-diagnosed pulmonary tuberculosis (PTB).

Materials and Methods. 109 patients with newly-diagnosed PTB were examined. All patients underwent a comprehensive medical examination, immunological blood tests, determination of the parameters of the oxidative stress-antioxidant defense system. Patients were divided into three main groups, depending on the level of alcohol consumption. Patients in each of the three groups were further divided into two subgroups depending on the treatment regimen. Statistical analysis was performed using the STATISTICA program.

Results. In patients who received standard therapy, increased alcohol consumption was associated with a decrease in the positive changes of the majority of inflammation and immune status indicators. This trend, in particular, was observed with regard to the progress of the decay cavities closure, persistence of cough complaints, changes in indicators of the immune-inflammatory (CRP, CD8+, CD4/CD8, PAMW, IPC) and oxidative status (SOD, GPX) ($p \leq 0.05$). After the antioxidants had been added, the best improvement of immune-inflammatory and oxidative status was observed in group 2 ($p \leq 0.05$). Additional antioxidant therapy in patients with newly-diagnosed PTB, regardless of alcohol consumption, contributed to better positive dynamics of cellular immunity, oxidative stress, and endogenous intoxication.

Conclusions. The addition of antioxidant drugs to the standard therapy of patients with newly-diagnosed PTB was accompanied by improved clinical and radiological, oxidative and immune-inflammatory parameters. Antioxidant therapy in such patients, regardless of the initial level of alcohol consumption, promoted better positive dynamics of phagocytic and enzymatic activity of neutrophils, oxidative stress, and endogenous intoxication. The best changes in immune-

inflammatory and oxidative status among patients taking antioxidants were observed in those who took alcohol at a health-threatening level.

Keywords: tuberculosis, alcohol consumption, antioxidants, immunity, oxidative stress.

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ВПЛИВ АНТИОКСИДАНТНОЇ ТЕРАПІЇ НА ДИНАМІКУ КЛІНІЧНИХ ТА ЛАБОРАТОРНИХ ПОКАЗНИКІВ У ХВОРИХ НА ТУБЕРКУЛЬОЗ ЛЕГЕНЬ, ВЖИВАЮЧИХ АЛКОГОЛЬ

Мета. Визначення впливу антиоксидантів на клінічні та лабораторні показники у хворих, що вживають алкоголь, із вперше діагностованим інфільтративним туберкульозом легень (ВДТБЛ).

Матеріали та методи. Обстежено 109 хворих чоловіків з ВДТБЛ. Усім пацієнтам проведене комплексне обстеження, імунологічні дослідження крові, визначення параметрів системи оксидативний стрес–антиоксидантний захист. Пацієнтів, залежно від рівня вживання алкоголю, поділено на три основні групи. Хворі кожної з трьох груп додатково розділені на дві підгрупи залежно від схеми лікування. Статистичний аналіз проведено за допомогою програми STATISTICA.

Результати. Пацієнти, які отримували стандартну терапію, при збільшенні рівня споживання алкоголю мали зменшення позитивної динаміки переважної більшості показників запалення та імунного статусу. Така тенденція, зокрема, спостерігалася у динаміці закриття порожнин розпаду, збереженні скарг на кашель, зміні показників імунозапального (СРБ, CD8+, CD4/CD8, ПСММ, ІЗФ) та окисного статусів (СОД, GPX) ($p \leq 0,05$). При додаванні антиоксидантів краща динаміка показників імунозапального та окисного статусів спостерігалась у групі 2 ($p \leq 0,05$). Додаткова терапія антиоксидантами у хворих на ВДТБЛ, незалежно від рівня вживання алкоголю, сприяла кращій позитивній динаміці показників клітинного імунітету, окисного стресу та ендогенної інтоксикації.

Висновки. Включення антиоксидантних препаратів до схеми стандартної терапії хворих ВДТБЛ супроводжуються поліпшенням клініко-рентгенологічних, окислювальних і імунозапальних параметрів. Терапія антиоксидантами у таких хворих, незалежно від вихідного рівня вживання алкоголю, сприяє кращій позитивній динаміці показників фагоцитарної та ферментативної активності нейтрофілів, окисного стресу та ендогенної інтоксикації. Найкраща динаміка імунозапального та окисного статусів серед пацієнтів, які отримували антиоксиданти, спостерігалась у пацієнтів, які вживали алкоголь на загрозливому здоров'ю рівні.

Ключові слова: туберкульоз, вживання алкоголю, антиоксиданти, імунітет, оксидативний стрес.

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INTRODUCTION / ВСТУП

Pathogenetic therapy is an important step in the comprehensive treatment of tuberculosis. It is designed to accelerate the reversal of inflammation, restore an adequate immune response, strengthen reparative processes in the body, prevent the formation of severe residual changes, as well as prevent adverse toxic reactions to anti-TB drugs and maintain continuity of treatment [1, 2]. The administration of pathogenetic therapy should be based on the results of a comprehensive analysis of the patient's condition, which takes into account the clinical and radiological form of tuberculosis, features of clinical course and pathomorphosis, depending on the immune system, free radical oxidation and antioxidant defense, metabolism and energy.

An important factor in the treatment of tuberculosis is restoring the regular activity of the monocyte-macrophage system; its functional failure leads to disorders of tuberculosis granuloma formation, elimination of mycobacteria and the progression of the tuberculosis process. No less important in the pathogenetic therapy of tuberculosis is the restoration of an adequate prooxidative and antioxidant processes balance. Free radical oxidation, leading to the formation of reactive oxygen species (ROS), is a protective mechanism aimed at destroying mycobacteria. ROS are involved in bioenergetic processes, homeostasis maintenance, oxidation and detoxification of exogenous and endogenous compounds and are able to influence immune responses.

However, Mycobacteria tuberculosis possesses a unique system of enzymatic antioxidant protection, which in combination with antioxidant factors of the cell wall, makes them very resistant to bactericidal radical factors generated by phagocytic cells of the macroorganism. The prevalence of prooxidation over antioxidant defense, provided by the activity of intracellular enzymes – superoxide dismutase, catalase, enzymes of the redox system of glutathione, can lead to the formation of severe tuberculosis with pronounced necrotic phenomena of tissues, accompanied by the formation of decay cavities and massive bacterial excretion [3–7].

Objective. The objective of our study was to determine the effect of antioxidant drugs, added to standard therapy during the intensive phase of treatment, on the clinical and laboratory parameters of alcohol-consuming patients with infiltrative newly-diagnosed pulmonary tuberculosis (PTB).

Materials and methods. In order to achieve the goal of the study, 109 male patients aged 20 to 50 years with an infiltrative form of newly-diagnosed PTB were examined. The median age was 37.00 years. All patients underwent a comprehensive general clinical, instrumental, and laboratory examination: history collection, determination of anthropometric characteristics and objective status of the patient, sputum examination, X-ray examination, assessment of alcohol consumption, clinical, biochemical and immunological blood tests, determination of parameters of the system "oxidative stress-antioxidant defense" (OS-AOD), evaluation of phagocytic activity of neutrophilic granulocytes.

The diagnosis of newly-diagnosed PTB was verified in accordance with the recommendations of the Order of the Ministry of Health of Ukraine dated 25.02.2020 № 530 "On Approval of Health Standards for Tuberculosis". The Alcohol Use Disorders Identification Test (AUDIT) was used to assess alcohol consumption.

All studies were conducted in accordance with the Declaration of Helsinki. The principle of voluntary participation of the respondents in the study was observed: the patients were informed about their right to refuse to participate, and in case of obtaining consent, the study participants were guaranteed complete anonymity.

Among the examined patients, three groups of patients were formed depending on the level of

alcohol consumption: group 1 (n = 34) – patients with newly-diagnosed PTB and low alcohol consumption (0–7 points on the AUDIT test), group 2 (n = 44) – patients who consumed alcohol with a health risk (8–15 points), group 3 (n = 31) – patients who abused alcohol or had a possible alcohol addiction (≥ 16 points).

According to the study design, patients in each of the three groups were divided into two subgroups depending on the treatment regimen (Tr1 and Tr2), which were administered for 2 months of the intensive phase of anti-TB therapy. Subgroup Tr1 included patients receiving standard therapy (isoniazid + rifampicin + pyrazinamide + ethambutol). Patients of subgroup Tr2, additionally to standard therapy, received antioxidant drugs according to the developed scheme: preparations of selenium and vitamin E in doses of 250 mg and 200 mg, respectively, once a day. Treatment subgroups were matched for age, the number of patients with bacterial excretion by smear, the prevalence of tuberculosis and the number of cases with destructive processes in the lungs.

Statistical analysis was performed using the software package Excel for Windows and STATISTICA. Methods of parametric and nonparametric statistics were used. The normality of the distribution of quantitative indicators was assessed using the Kolmogorov–Smirnov criterion. Evaluation of the treatment effectiveness was performed in a comparative analysis of the median percentage of the dynamics of indicators after treatment in each group. The Mann–Whitney test was used to compare the main parameters of the groups. For all types of analysis, the critical significance level for the statistical criteria was 0.05.

Results. A comparative analysis of the clinical and laboratory parameters changes was performed between groups of patients with different levels of alcohol consumption to assess the change in indicators in clinical groups, depending on the therapy received. The comparative analysis was performed separately among individuals receiving standard therapy and patients receiving additional antioxidants.

Analysis of the radiological picture among the comparison groups depending on the received therapy showed that patients of subgroup Tr1, who consumed alcohol at low levels, had significantly more cases of decay cavities closure after two months of treatment compared with groups 2 and 3 (p = 0.02). There was no statistically significant difference in the number of decay cavities closure between subgroups Tr1 of groups 2 and 3 (p = 0.07). In contrast, in the subgroup of treatment Tr2, the picture differed: in groups 1 and 2, there was a 100% progression of closure of the decay cavities, and in group 3, this value equaled 66.7% (Figure 1).

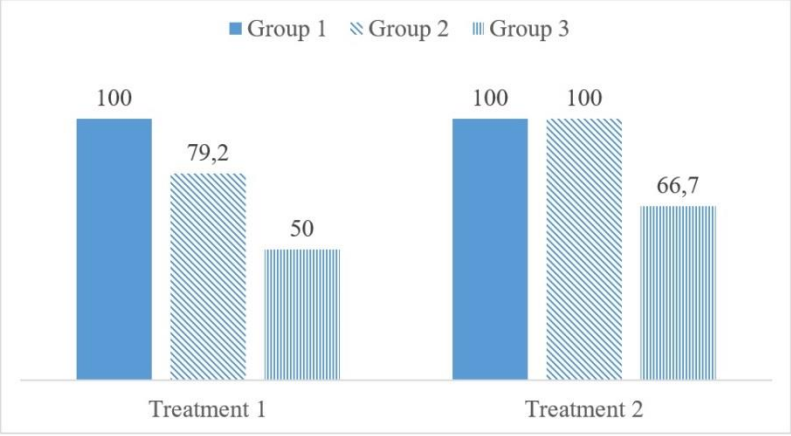

Figure 1 – The percentage of the decay cavities closure among groups of patients depending on the therapy received after two months of treatment

When comparing groups on the basis of the cessation of bacterial excretion, no statistically significant differences were found in both subgroup of treatment. At the same time, in patients with low and health-threatening levels of alcohol consumption, bacterial excretion was observed in 100% of cases, and in patients who abuse alcohol, bacterial excretion was detected in 86.67% of cases (p > 0.05).

The analysis of the persistence of complaints after two months of treatment revealed that in subgroup Tr1 in group 1, patients had significantly fewer cough and sputum complaints than in groups

2 and 3 ($p \leq 0.01$). The genesis of the onset and persistence of these complaints during the treatment may not be related to the tuberculosis process, as patients in groups 2 and 3 smoked statistically more often than in group 1 ($p < 0.05$).

Among patients receiving the standard treatment regimen, the best increase in BMI was recorded in group 2 (1.70%). The dynamics of weight gain in this group was 1.42 times higher than in group 3 ($p = 0.56$) and 1.72 times higher than in patients of group 1 ($p < 0.01$). In patients who received additional antioxidants, the best indicators of BMI dynamics were determined in group 3 (2.30%), which is 1.35 times higher than in group 2 ($p = 0.05$) and 2.32 times more, compared with group 1 ($p < 0.01$).

A comparative analysis of changes in immune-inflammatory status in groups of patients receiving standard therapy found that the best positive dynamics in the predominant number of indicators had patients in group 1.

The dynamics of CRP levels, peptides of average molecular weight (PAMW) and the result of nitro blue tetrazolium reduction test spontaneous (NBTsp) in this group were significantly higher than in patients of groups 2 and 3 ($p < 0.05$). It was also determined that in group 3, compared to the first two groups, patients had worse dynamics of recovery of CD8, immune-regulatory ratio, phagocytosis completion index (PCI), average cytochemical coefficient both spontaneous and stimulated (ACC (sp) and ACC (st)) ($p \leq 0.05$).

The effect of standard TB therapy on the OS-AOD system indicators, as a whole, had a positive effect in all three study groups. Patients who consumed low levels of alcohol had better positive changes in all parameters of antioxidant defense, but a significant difference was observed only in the intensity of the changes of superoxide dismutase (SOD), compared to groups 2 and 3 ($p = 0.03$), and glutathione peroxidase (GPX), compared to group 3 ($p = 0.02$). There were no statistical differences between clinical groups in the indicators of oxidative stress.

Patients, who received additional antioxidant therapy, after intensive phase treatment also showed positive dynamics of inflammatory and immune status. However, in this cohort, the best effect after 2 months of treatment was determined in the group of patients who drank alcohol with a health risk. At the same time, there was a leveling of the difference in the dynamics of indicators between the groups of patients who consumed alcohol at a low level and alcohol abusers. Patients in group 3 had better dynamics of erythrocyte sedimentation rate (ESR). The percentage of dynamics in this group was 1.38 and 1.35 times higher, respectively, than in patients of groups 1 and 2 ($p \leq 0.03$). Also in group 3 there was a better growth of IPC compared to the first two groups ($p \leq 0.05$). The decrease in the level of PAMW in the blood was most significant in group 2 when compared to other groups ($p \leq 0.02$). Among patients with low alcohol consumption, the smallest increase in ACC (st) was observed: 1.31 and 1.30 times lower, respectively, than in groups 2 and 3 ($p < 0.01$). According to other indicators of immune-inflammatory status, no significant differences between the groups were found.

A comparative analysis of oxidative status in patients receiving additional antioxidants showed that the best positive dynamics was demonstrated by patients in group 2. There were no significant differences in the indicators of the antioxidant defense system between groups, but the decrease in oxidative stress in group 2 was statistically higher than in other clinical groups ($p \leq 0.02$), indicating a better response of patients in this group to the addition of pathogenetic therapy. The lack of a significant difference in the intensity of the dynamics of indicators between groups 1 and 3 is also positive, because we can assume that individuals who had the greatest imbalance of OS-AOD system before treatment (group 3) still responded to treatment, compared with patients having the slightest disturbances in oxidative status (group 1).

To determine the effect of antioxidant therapy on the effectiveness of treatment and the dynamics of clinical and laboratory parameters in patients with newly-diagnosed PTB, regardless of the initial level of alcohol consumption, two general cohorts were formed among the studied patients on the basis of the received therapy. The Tr1 cohort ($n = 57$) consisted of patients receiving standard TB therapy, and the Tr2 cohort ($n = 52$) included patients taking additional antioxidants.

The BMI increase in group Tr2 was significantly higher than in group Tr1 ($p = 0.04$). On the basis of the decay cavities closure, there was a rather significant trend, in which this indicator was almost significantly higher in the Tr2 group. In group Tr1 in control radiography after the intensive phase of treatment, signs of lung tissue destruction remained in 13 people, and in group Tr2 - only in 5 patients ($p = 0.0567$) (Figure 2).

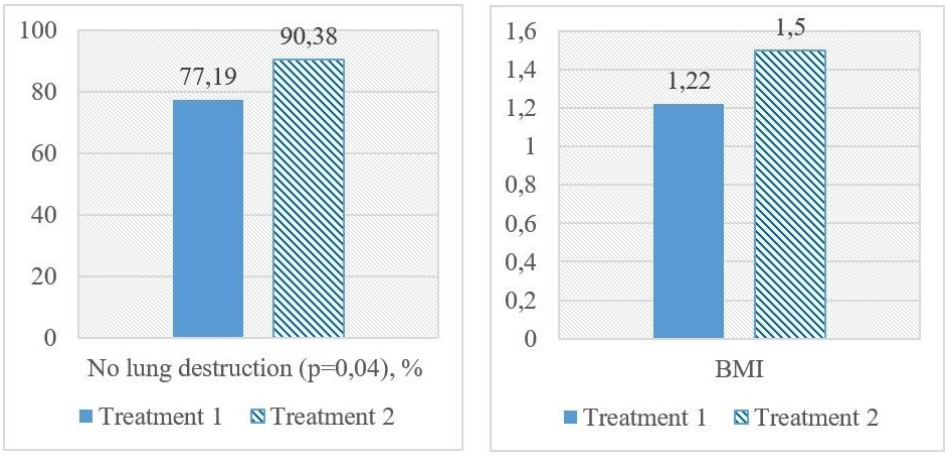

Figure 2 – The level of the decay cavities closure and the dynamics of BMI in the generalized groups depending on the therapy received after two months of treatment

Comparative analysis of the dynamics of complaints, other general clinical and radiological data, QOL indicators and sputum studies between these groups did not reveal statistically significant differences ($p > 0.05$).

A comparative analysis of inflammatory, immunological and oxidative profiles revealed that patients who received antioxidant therapy, in general, had more significant positive changes in the vast majority of parameters. The dynamics of CRP level in group Tr2 was 1.57 times higher compared to group Tr1 ($p < 0.01$). The reduction in blood PAMW levels among patients taking antioxidants was 1.71 times higher than in patients receiving standard therapy.

Indicators of enzymatic activity of granulocytic neutrophils during treatment also had a more pronounced positive trend among patients taking antioxidants. The dynamics of the IPC, NBT sp, NBT st levels, phagocytosis stimulation index (PSI), ACCsp and ACCst were higher in group Tr2 relative to group Tr1, respectively, in 1.75, 1.61, 1.76, 1.81, 1.42 and 1.91 times ($p \leq 0.01$) (Figure 3).

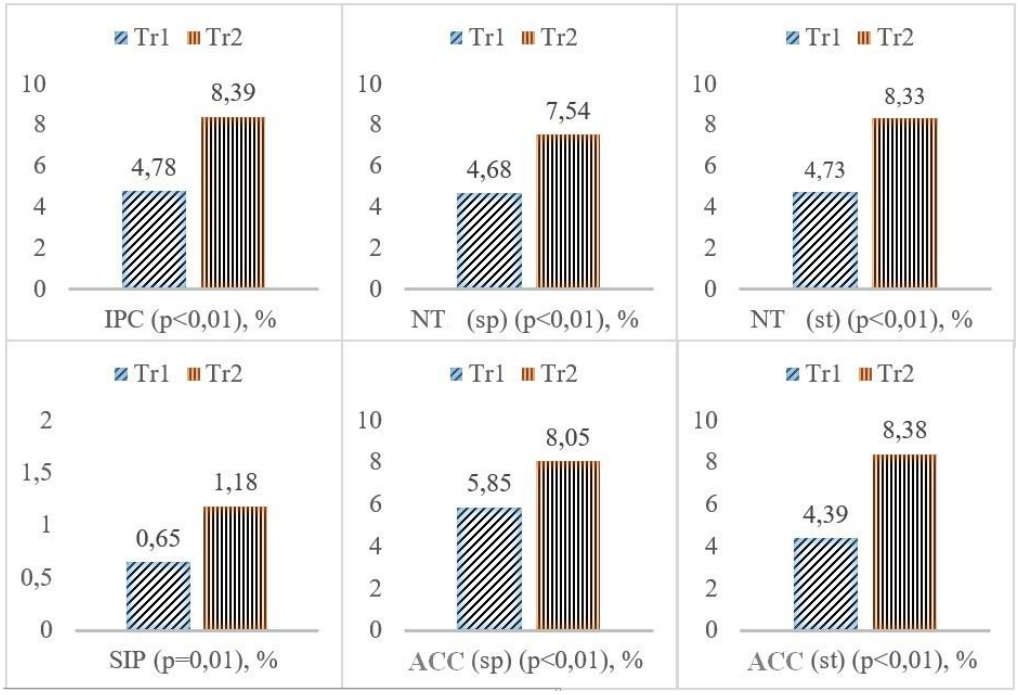

Figure 3 – Dynamics of phagocytic and enzymatic activity of phagocytes in groups depending on the received therapy after two months of treatment (IPC – index of phagocytosis completeness, NBT (sp, st) – nitroblue tetrazolium test (spontaneous, stimulated), SIP – stimulation index of phagocytosis, ACC (sp, st) – average cytochemical coefficient (spontaneous, stimulated))

A similar picture was observed in the change of the levels of parameters of the OS-AOD system. The change in AOD indicators between groups was generally positive and had no statistically significant differences, but the decrease in OS parameters in group Tr1 was significantly less intense compared to group Tr2. The decrease in the level of diene conjugates (DC) in the blood among patients of group Tr2 was 1.77 times higher, the reactive substances of thiobarbituric acid (TBA-RS) – 1.85 times, NO3 – 2.06 times and NO2 – 1.55 times, compared with patients receiving standard anti-TB therapy ($p < 0.01$) (Figure 4).

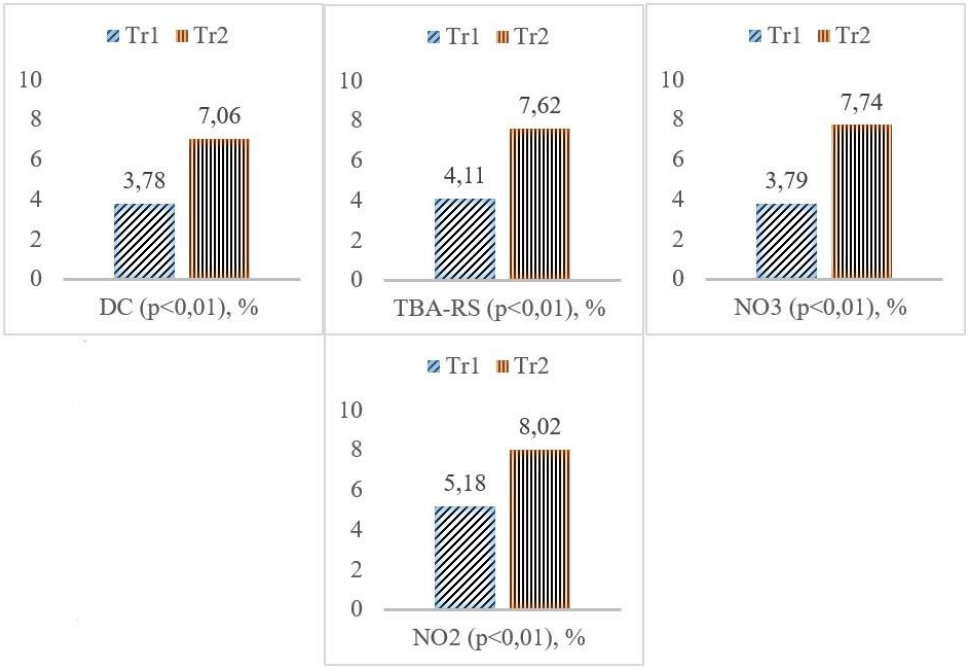

Figure 4 – Indicators of oxidative stress in general groups depending on the received therapy after two months of treatment (DC – diene conjugates, TBA-RS – thiobarbituric acid-reactive substances)

Discussion. Summarizing the results of a comparative analysis of patients with newly-diagnosed PTB and different levels of alcohol consumption, depending on the therapy, we saw that among patients who had standard therapy, the positive changes of the vast majority of indicators decreased along with the increased alcohol consumption,. This trend, in particular, was observed in the progression of decay cavities closure, persistence of cough complaints, changes in immune-inflammatory (CRP, CD8+, CD4/CD8, PAMW, IPC) and oxidative status (SOD, GPX).

After antioxidants had been added to the treatment regimen for 2 months, the best improvement of immune-inflammatory and oxidative status was observed in group 2. Also, a comparative analysis between groups 1 and 3 showed that antioxidant therapy had a significant positive effect on patients who abused alcohol. There was no significant difference found in almost all parameters among these groups. Moreover, the dynamics of IPC and ACC (st) in group 3 was significantly better compared to group 1 ($p \leq 0.01$).

After analyzing the comparative analysis data, it can be noted that additional antioxidant therapy during intensive phase treatment in patients with newly-diagnosed PTB, regardless of the initial level of alcohol consumption, contributed to better positive dynamics of cellular immunity, including phagocytic and enzymatic activity of neutrophils, oxidative stress and endogenous intoxication (PAMW, CRP).

Limitations of the study. The presented study fragment aimed to conduct a comparative characteristic analysis of the additional pathogenetic therapy with antioxidants during the intensive phase of treatment and its effectiveness on the clinical and laboratory status of patients with newly-diagnosed TB who drink alcohol. However, our study highlighted changes mainly from the cellular part of the immune system. The plan of further research aims to study the reaction of indicators of the humoral immunity to addition of antioxidants in patients with newly-diagnosed PTB in the conditions of alcohol consumption.

CONCLUSIONS / ВИСНОВКИ

Inclusion of selenium and vitamin E in daily doses of 100 mg and 200 mg in the standard therapy scheme for patients with newly-diagnosed PTB for 2 months of intensive phase treatment is accompanied by improvement of clinical and radiological, oxidative and immune-inflammatory parameters. Additional antioxidant therapy in such patients, regardless of the initial level of alcohol consumption, contributed to better positive changes in cellular immunity, including phagocytic and enzymatic activity of neutrophils, oxidative stress, and endogenous intoxication. A comparative analysis of the changes in the studied indicators in the groups of patients with different levels of alcohol consumption revealed that the best improvement of immune-inflammatory and oxidative status among the patients with administrated antioxidants was observed in patients who consumed alcohol at a dangerous level.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

FUNDING / ДЖЕРЕЛА ФІНАНСУВАННЯ

None.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

Ivan Hrek – a significant contribution to the design or construction of the manuscript; obtaining, analyzing or interpreting data for the manuscript, drafting the manuscript, agreeing to be responsible for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are properly investigated and resolved.

Maryna Kochuieva – significant contribution to the design or construction of the manuscript; final approval of the version to be published; agree to be responsible for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are properly investigated and resolved.

Valentyna Psarova – drafting the manuscript or critical revision of its important intellectual content; agree to be responsible for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are properly investigated and resolved.

Gennadiy Kochuiev – drafting the manuscript or critical revision of its important intellectual content.

Anton Rogozhyn – analysis or interpretation of data for the manuscript; agree to be responsible for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are properly investigated and resolved.

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