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CLINICAL, LABORATORY AND RADIOLOGICAL ASSOCIATIONS WITH EXTENDING OF THE INTENSIVE PHASE OF TREATMENT IN PATIENTS WITH FIRST DIAGNOSED INFILTRATIVE PULMONARY TUBERCULOSIS

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Despite the availability of medical services, timely detection of pulmonary tuberculosis, before the appearance of destructive changes, is often difficult. The management of patients with an infiltrative form in a hospital setting does not always guarantee the same positive effect and sometimes requires prolongation of therapy. The effectiveness of therapy can be associated with various factors and is of interest to study.

***The aim of this work** was to study the effectiveness of standard therapy in patients with first diagnosed infiltrative pulmonary tuberculosis, clinical laboratory and radiological associations with prolongation of the intensive phase of treatment.*

***Materials and methods**. The study involved 109 men from 18 to 53 years old with first diagnosed infiltrative pulmonary tuberculosis with preserved MBT sensitivity to 1-st line anti-tuberculosis drugs. Patients were examined before and after 60 doses of the intensive phase of treatment, after which two groups were formed. Group 1 included patients with pronounced positive clinical and radiological dynamics, who entered the continuation phase of therapy. Group 2 included patients with insufficient clinical and radiological dynamics, for whom the intensive phase of treatment was extended to 90 doses.*

***Results**. Weak dynamics in patients who needed prolongation of treatment was associated with the characteristics of the initial data of patients in this group compared with similar indicators in Group 1. These were a reliably higher frequency of symptoms of intoxication and coughing, a reliably greater number of patients excreting mycobacterium tuberculosis in large quantities in sputum, with reliably high blood concentrations of haptoglobin and ceruloplasmin levels.*

***Conclusions**. Patients requiring prolongation of the intensive phase of treatment are characterized by an initially higher prevalence of infiltrative changes in the lungs, a small number of lung lesions limited to 2 segments, the presence of destructive changes in 100 % of cases, and a significant increase in the factors of the systemic inflammatory response*

***Keywords**: infiltrative pulmonary tuberculosis, effectiveness of treatment, extending the intensive phase of treatment, clinical laboratory and radiological associations*

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1. Introduction

Mycobacterium tuberculosis (MBT) is a causative agent of an infectious disease that has perfected its art of survival in human communities since ancient times [1]. Despite significant efforts by WHO to introduce modern methods of combating this pathology, the global incidence of tuberculosis is decreasing annually by only 1.5 %, which does not correspond to the expected projections [2].

With the improvement in the availability of medical care, it became possible to detect pulmonary tuberculosis at the stage of focal and infiltrative changes [3, 4]. At the present time, it is the infiltrative form of tuberculosis that occupies a leading position in the structure of new cases of diseases and therefore is of the greatest interest [5].

Approaches in the diagnosis of tuberculosis have not practically changed in recent years [6]. The need for annual screening of the population to identify persons with changes in the lungs is discussed, which is due to the significant costs from the state budget for examinations [4]. Taking into account the fact that tuberculosis is not only an infectious, but also a social disease in many countries, it was proposed to conduct an X-ray examination in groups with a high risk of this pathology morbidity [7]. Most of these groups are people with socio-economic problems, which serves as a complicating factor for attracting them to the survey [8]. In this regard, the detection of active tuberculosis in the early stages of the disease is often difficult, which leads to an increase in the number of common forms with significant destructive

changes in the lungs [9]. Treatment for these forms of tuberculosis is not always effective. It is often longer and requires more careful monitoring of the course of the disease [10]. The occurrence of relapses is associated with the development of resistance, which dictates the need for strict adherence to the treatment regimen for a first diagnosed tuberculosis process (FDTB) and careful monitoring of the dynamics of the disease to prevent recurrent course [11].

Despite the standardization of treatment for pulmonary TB, its effectiveness may vary, and some patients may need to extend treatment. The effectiveness of therapy can be associated with genetic and environmental factors, the characteristics of the activity of the factors of the systemic inflammatory response, the state of the immune system, and a few other indicators [12].

The aim of the work. Considering the paucity of data on the determinants of prolongation of the intensive phase (IF) of treatment of patients with pulmonary tuberculosis, a study was undertaken, the purpose of which was to study the effectiveness of standard therapy in patients with infiltrative first diagnosed pulmonary tuberculosis (IFDPTB), clinical laboratory and radiological associations with prolongation of the IF of treatment.

2. Materials and methods of the research

The study was carried out based on the Public Non-Profit Enterprise of the Kharkiv Regional Council "Regional TB Dispensary No. 7" in the period 2019–2021. The study involved 109 men from 18 to 53 years old (38.98±8.96 years old) diagnosed with IFDPTB with preserved MBT sensitivity to 1-st line anti-tuberculosis drugs. The patients were examined before and after 60 doses of IF treatment. According to the effectiveness of therapy, the patients were divided into 2 groups. Group 1 consisted of patients with positive clinical and radiological dynamics (n=81), who proceeded to the next stage of treatment – the continuation phase (CP). In patients with insufficient clinical and radiological dynamics (n=28), IF was prolonged to 90 doses (Group 2).

Inclusion criteria in the study: men of working age, culture-confirmed sensitive pulmonary tuberculosis, infiltrative type of radiological changes in the lungs.

Exclusion criteria: acute and chronic comorbidities that could seriously affect the study results (COPD, bronchial asthma, liver and kidney disease, diabetes mellitus, cardiovascular disease, HIV; mental illness, alcohol and drug abuse).

The work was carried out in accordance with the principles of the Declaration of Helsinki adopted by the General Assembly of the World Medical Association (1964–2000), the Council of Europe Convention on Human Rights and Biomedicine (1997), relevant WHO provisions, the International Council of Medical Societies, the International Medical Code ethics (1983) and laws of Ukraine

Informed consent was obtained from all patients who participated in the study. The Committee of the Bioethics Commission approved and confirmed the protocol No. 3 dated 12.10.2021.

The patients underwent a standard comprehensive study of clinical, laboratory and radiological parameters in accordance with the protocol for the management of tuberculosis patients [13]. Additionally, we investigated the indicators of the systemic inflammatory response: the level of ceruloplasmin in the blood (by the Ravin method) and the level of haptoglobin (reactions with rivanol) using standard reagent kits ("Reagent" Ukraine).

Mathematical and statistical processing of the data obtained was carried out using Microsoft Excel 2003 and Statistica 6.0 programs. The significance of differences between the mean values was determined using the Mann-Whitney U-test. The assessment of the reliability of the correlation coefficient was carried out according to standard tables.

3. Research results

All examined patients were bacteria-excreting according to the data of the culture method of research. Massive bacterial excretion was detected in 58.7 % (n=64) of patients who had positive smear microscopy. Lung destruction during X-ray examination was found in 61.5 % (n=67) patients, limited infiltrative changes within two segments (SEG) of one lung – in 23.9 % (n=26), infiltrative changes outside two SEG of one lung – in 38.5 % (n=42), infiltrative changes in both lungs - in 37.6 % (n=41) patients.

Assessing the presence of bad habits, we determined that 79.8 % (n=87) of men noted a history of alcohol consumption, and 90.8 % (n=99) of patients confirmed smoking. When collecting the anamnesis, it was revealed that only 50.5 % (n=55) of the examined were married and only 45.9 % (n=50) of the patients had a permanent place of work.

Among the complaints, 76.1 % (n=83) of patients noted symptoms of intoxication, which manifested themselves in weakness, feeling of malaise, and rapid fatigue. Cough was noted by 50.4 % (n=55) of patients, and a decrease in appetite – by 75.2 % (n=82) of patients. When taking anamnesis, 40.4 % (n=44) of the subjects showed a decrease in body weight of more than 5 kilograms over the last 2 months.

Among the laboratory parameters, the high level of erythrocyte sedimentation rate (ESR) was noted, which averaged 27.2±12.7 mm/h. ALT and AST parameters before treatment had increased values of 0.9±0.5 μmol/L and 0.54±0.3 μmol/L, respectively. The levels of haptoglobin, ceruloplasmin, and C-reactive protein (CRP) were also outside the normal range and amounted to 2.4±0.9 g/L, 479.6±88.1 mg/L and 17.3±8 mg/L respectively. Attention was drawn to the tendency towards a decrease in the level of total protein in the blood (65.5±8 g/l) and its main fraction, albumin (37.6±3.5 g/l).

After receiving the standard 60 doses of therapy, 25.7 % (n=28) of patients required an extension of IF to 90 doses, which was associated with insufficient clinical and radiological dynamics (Group 2). The remaining 81 subjects switched to CP (Group 1). The dynamics of the studied clinical and laboratory parameters of patients before and after IF treatment in Group 1 is presented in Table 1.

After IF treatment in patients from Group 1, the number of patients with symptoms of intoxication, complaints of cough and loss of appetite significantly decreased, while massive bacterial excretion was not detected in any patient. Our attention was drawn to a pro-

nounced significant decrease in the level of systemic inflammatory response factors in the blood – haptoglobin, ceruloplasmin, and CRP (Table 1).

The dynamics of the studied clinical and laboratory parameters of patients before and after IF treatment in Group 2 is presented in Table 2.

Table 1

Features of the dynamics of clinical and laboratory parameters in patients of Group 1

Indicator	Before IF	After IF	p
Body temperature, ^oC	37.2±0.4	36.7±0.4	p<0.001
BMI, kg/m^2	19.9±1.8	20±1.8	p=0.018
Erythrocytes, 10^{12} cells/l	3.75±0.5	3.8±0.4	p=0.03
Hb, g/l	137.8±16.7	142.3±13.3	p=0.04
ESR, mm/h	26±12.8	18.7±8.2	p<0.001
WBC, 10^9 cells/l	6.8±1.8	6.4±1.2	p=0.043
Segmented neutrophil, %	62.5±6	61.5±4.2	p=0.167
Lymphocyte, %	27.2±5.6	30.8±4.2	p<0.001
Monocytes, %	4.4±2	5.5±2.1	p<0.001
Total protein, g/l	66.8±7.7	68.3±6	p=0.034
Albumin, g/l	38±3.7	38.6±2.8	p=0.066
Urea, mmol/l	5.8±2.1	5.2±1.6	p=0.029
ALT, μmol/l	0.84±0.49	0.77±0.37	p=0.026
AST, μmol/l	0.51±0.25	0.48±0.23	p=0.021
Haptoglobin, g/l	2.1±0.8	1.7±0.6	p<0.001
Ceruloplasmin, mg/l	463.7±88.9	426±70.6	p=0.001
CRP, mg/l	17.2±7.8	6.3±3.3	p<0.001

Table 2

Features of the dynamics of clinical and laboratory parameters in patients of Group 2

Indicator	Before IF	After IF	p
Body temperature, ^oC	37.3±0.6	37±0.5	p<0.001
BMI, kg/m^2	18.9±1.6	19±1.6	p=0.036
Erythrocytes, 10^{12} cells/l	3.68±0.4	3.76±0.3	p=0.037
Hb, g/l	132.7±10.9	135.1±7.4	p=0.24
ESR, mm/h	30.8±12.2	25.1±7.8	p=0.009
WBC, 10^9 cells/l	7.7±1.8	7.1±1.2	p=0.052
Segmented neutrophil, %	62.2±6.1	64.5±4	p=0.031
Lymphocyte, %	24.1±6.1	24.3±4.2	p=0.89
Monocytes, %	4.8±2	5.6±1.8	p=0.156
Total protein, g/l	61.4±7.7	64.1±7.2	p=0.038
Albumin, g/l	36.4±2.6	37.7±3.4	p=0.081
Urea, mmol/l	6.7±2.2	5.7±2	p=0.035
ALT, μmol/l	1.09±0.42	0.98±0.32	p=0.159
AST, μmol/l	0.63±0.29	0.58±0.19	p=0.141
Haptoglobin, g/l	3.2±0.8	2.6±0.6	p<0.001
Ceruloplasmin, mg/l	528.4±65.4	495±70.8	p=0.038
CRP, mg/l	17.7±8.6	9.7±4.6	p<0.001

In Group 2, after IF treatment, the number of patients with symptoms of intoxication, cough, and decreased appetite was significantly greater than in Group 1, which indicated a lower treatment efficacy, while 21.4 % (n=6) of patients remained massive bacterial excretors. The dynamics of blood levels of systemic inflammatory response factors was positive and reliable.

The dynamics of the studied parameters in patients of both groups generally indicated a favourable effect of the treatment on the clinical and laboratory status of patients, but less in Group 2. The dynamics of the number of patients with destructive changes in the lungs after 60 doses of IF therapy, depending on the prevalence of the infiltrative process, are shown in Fig. 1, 2.

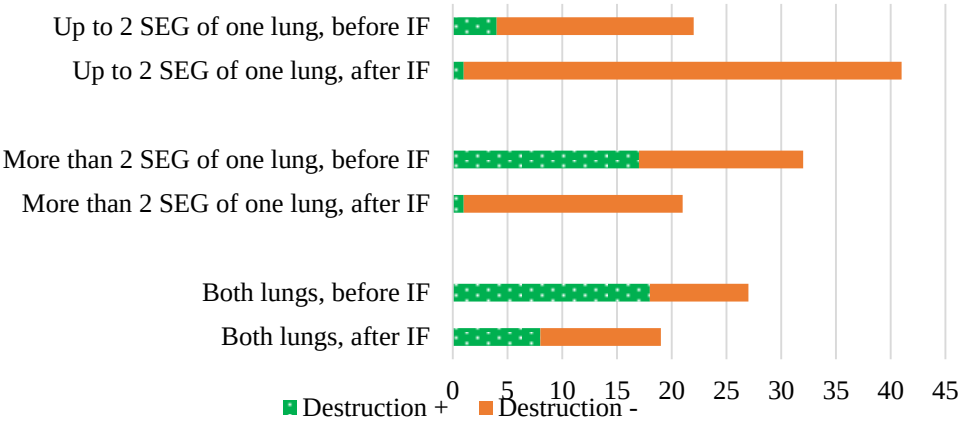

Fig. 1. Dynamics of the number of patients in Group 1 with destructive changes in the lungs after 60 doses of IF therapy, depending on the prevalence of the infiltrative process

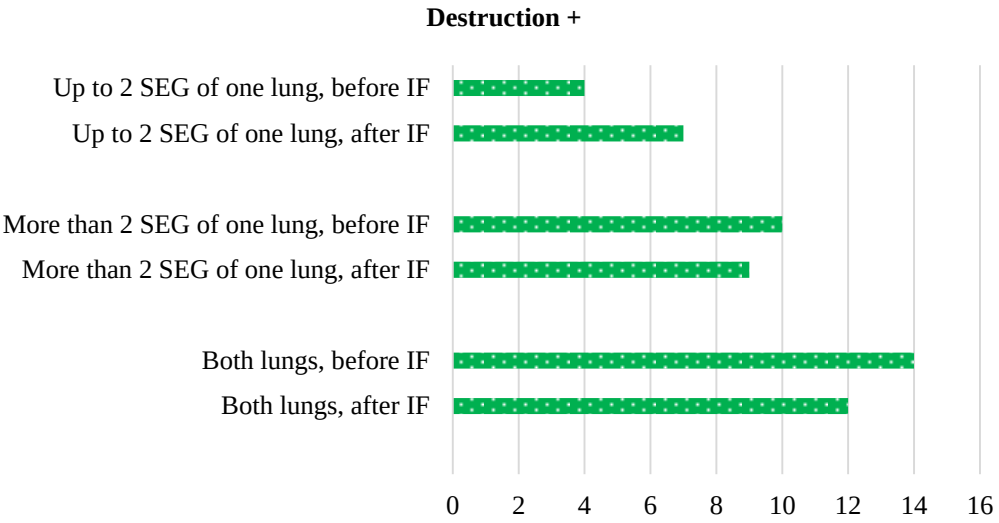

Fig. 2. Dynamics of the number of patients in Group 2 with destructive changes in the lungs after 60 doses of IF therapy, depending on the prevalence of the infiltrative process

Since patients from Group 2 retained decay cavities in the lungs before and after IF treatment, we do not observe the dynamics of a decrease in this indicator.

4. Discussion

All patients included in the study were divided into 2 groups according to the degree of clinical and laboratory and radiological dynamics, patients in Group 2 had clearly insufficient, but positive dynamics of clinical and laboratory parameters and were characterized by the presence of destructive changes in the lungs in 100 % of patients, which required prolongation of treatment up to 90 doses.

From the presented initial data, special attention is drawn to the percentage of massive bacterial excretion, when we can detect MBT by microscopy. The distribution of this indicator among the study groups clearly demonstrates its connection with the slow course of the pathological process in Group 2, where massive bacterial excretion was 1.6 times more frequent.

When assessing radiological parameters before treatment, there is a significant predominance of destructive changes in patients of Group 2. Also, the low incidence of limited infiltrative changes in the lungs that do not go beyond two SEG in Group 2 gives us a clear idea of the value of this parameter as prognostically important relatively fewer positive dynamics of therapy [14]. In Group 2, half of the patients had a widespread infiltrative process in both lungs (versus 24.8 % in Group 1).

Slow dynamics in patients of Group 2 was associated with the characteristics of the initial data of patients in this group compared with similar indicators in Group 1 – with a significantly higher frequency of symptoms of intoxication and coughing, with a significantly greater number of massive bacterial excretors, with significantly higher blood concentrations of haptoglobin and ceruloplasmin levels.

Study limitations. This study was limited to the first period of treatment for tuberculosis – the intensive phase, the lack of in-depth laboratory research methods to assess disorders of the immune status and psychological state of patients.

Prospects for further research. Study of immune status and phagocytic activity of neutrophils in patients with

FDTB during the intensive phase of treatment. Continue to monitor patients throughout the treatment period.

5. Conclusions

Most of the patients with IFDPTB were characterized by positive dynamics of clinical, laboratory and radiological parameters after 60 doses of IF treatment, while a quarter of patients required prolongation of therapy to 90 doses. Patients requiring prolongation of IF treatment were characterized initially by a higher prevalence of infiltrative changes in the lungs, a small number of lung lesions limited to 2 SEG, and the presence of destructive changes in 100 % of cases.

Prolongation of IF treatment in patients with IFDPTB was associated with massive bacterial excretion, a high frequency of respiratory symptoms and signs of intoxication, as well as a significant increase in the factors of the systemic inflammatory response – haptoglobin and ceruloplasmin

Conflict of interests

The authors declare that they have no conflicts of interest.

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