THE ROLE OF TUMOR NECROSIS FACTOR IN THE DEVELOPMENT OF CACHEXIA IN PATIENTS WITH CHEMORESISTANT TUBERCULOSIS.

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According to the research of many scientists [21, 23] and WHO [25] tuberculosis is an epidemic disease all over the world these days, especially its drug-resistant version [13]. In general, a dangerous situation for mankind is created by the cases of tuberculosis of MDR [16] and XDR [4], when they sometimes show greater resistance to anti-tuberculosis drugs, or when the patients have uncorrected side effects [10]. Thus, conditions for the appointment of palliative treatment for these categories of tuberculosis can be formed [14, 17].

One of the major problems in the treatment of tuberculosis is the predominance of the catabolic processes over the anabolic ones [15]. Most often this is manifested by a decrease in the body weight of the patient [2, 5, 11, 12].

An important role in the development of a specific process is given to the mechanisms of immunological disregulation [18, 19]. Changes in the immunity of chemoresistant pulmonary tuberculosis are associated with a decrease in the effectiveness of treatment [6]. Tumor Necrosis Factor - (TNF-alpha, or cachectin) [1] is synthesized by activated macrophages and has a cytotoxic effect, as well as immunomodulatory and anti-inflammatory effects [8]. TNF stimulates macrophages [24]. For some bacteria (including tuberculosis) macrophages are the "habitat" [20]. Having appeared as a result of phagocytosis in phagolysosomes, pathogens become

protected both from antibodies and from cytotoxic T-lymphocytes [9]. By suppressing the activity of lysosomal enzymes, these bacteria actively multiply inside the cell and thus become the cause of an acute infectious process [7].

In literature data indicate that TNF-alpha and cachexia [22] in specific tuberculous process may be predictable[3], but in cases of tuberculosis with palliative treatment it is not studied.

The purpose of this work was to assess the possibility of predicting the indicators of body mass deficit and the level of TNF in the blood drugs-resistant tuberculosis in patients with antitubercular treatment and without it (palliative care).

MATERIALS AND METHODS

A survey was conducted on 81 patients with CRTB of lungs that are being treated at the Zaporizhzhia Regional Hospital and a specialized tuberculosis hospital in the Sofiivka penitentiary establishment №55 of the Ministry of Justice of Ukraine in the Zaporizhzhia Region. All patients (100%) were males. Their average age was 40.1 ± 12.1 years. Patients were divided into 2 groups: the main group consisted of 52 patients who were receiving palliative care. Control group was formed of 29 patients receiving antimycobacterial therapy in category 4, in accordance with the profile of drug resistance tuberculosis as described in the Unified clinical protocol of medical care "Tuberculosis" (Order of the Ministry of Health of Ukraine № 620 of 04.09.2014) []., Comparison groups have been mapped by age and gender. All patients signed a patient’s informed written consent to participate in the study.

Investigation of TNF-α level in serum was carried out using the Sirio S immuno-enzyme reader, using the kit of Bender MedSystems GmbH (Austria), (pg / ml) as well as a solid-phase enzyme-linked immunosorbent assay.

The Body Mass Index (kg/m^2) was applied to calculate the body weight index (BMI).

The results of the study are processed by modern methods of analysis on a personal computer using statistical software package of STATISTICA® for Windows 6.0 (Stat Soft Inc., AXXR712 D833214FAN5).

The normality of the distribution of quantitative characteristics was analyzed using the Shapiro-Wildlife test. Descriptive statistics are provided in the form of median with interquartile scope - Me [Q25; Q75] because the parameters had a distribution which was different from normal. The reliability of the differences in the comparable values was determined by Mann-Whitney test. All the tests were bi-directional. Statistically significant difference was considered for $p < 0,05$. Correlation analysis was performed using the Pearson correlation coefficient (r).

To determine the risk factors for progression, the χ^2 method using Yates's correction and Fischer's exact criterion for data, where the number of observations did not exceed 20, was used. Statistically significant results were considered where the error is $p < 0,05$. The ratio of chances to the influence of the identified factors on the progression of the disease was estimated. To confirm the statistical significance, confidence intervals (CI) were determined; if they did not contain a unit, the factor was considered to have an effect on progression.

RESULTS AND DISCUSSION

After evaluating the indicators included in the study, it was found that patients with drug-resistant tuberculosis of the lungs who received palliative care determined reliable changes in all parameters, in comparison with the group of patients receiving anti-tubercular treatment.

Table 1. TNFα indicators in patients with drug-resistant tuberculsis of lungs, depending on the type of treatment and BMI Level, Me [Q_{25}; Q_{75}]

Indicator	Main group (n=52)		Comparison group (n=29)		P1-2	P1-3	P3-4	P2-4
	BMI <18,5 (n=27)	BMI ≧18,5 (n=25)	BMI <18,5 (n=5)	BMI ≧18,5 (n=24)				
	1	2	3	4				
TNFα, pg/ml	620 (260; 1000)	80 (40; 80)	160 (120; 500)	80 (60; 80)	0,000	0,141	0,008	0,275
BMI, kg/m^2	16,8 (16,0; 17,3)	21,2 (19,9; 22,1)	17,67 (17,32; 18,17)	20,9 (20,1; 23,4)	0,000	0,079	0,001	0,608

Note: Main group - tuberculosis patients who received palliative therapy. Comparison group - tuberculosis patients who took anti-tubercular therapy.

Table 2. The calculation of the odds ratio with a 95% confidence interval in the table of conjugacy of the presence / absence (palliative) of anti-tubercular treatment of drug-resistant tuberculosis and body weight deficit.

	Palliative treatment of tuberculosis	Standart treatment of drugresistant tuberculosis	Together
Deficiency of body weight available (BMI<18.5 kg/m^2)	27	5	32

Deficiency of body weight is absent (BMI≥18.5 kg/m^2)	25	24	49
Together	52	29	81

The chance to find a risk factor in the main group is 5,400. The chance to find a risk factor in the control group is 1.042. Odds ratio (OR) 5,184. Standard mistake at odds ratio (S) is 0.565. The lower limit is 95% confidence interval (CI) 1,714. The upper limit is 95% confidence interval (CI) 15,675. At confidence intervals, 95% of the statistics can be considered reliable ($p < 0,05$).

Table 3. Criteria for assessing the significance of the difference in outcome depending on the effect of the risk factor for the presence / absence (palliative) of the anti-tubercular treatment and body weight deficit.

Name of the criterion	Value of the criterion	The level of significance
Criterion χ^2	9,370	$p<0,01$
Criterion χ^2 with Yeats correction	7,975	$p<0,01$
Criterion χ^2 corrected for probability	10,023	$p<0,01$
Fischer's exact criterion (two way)	0,00230	$p<0,05$
The minimum value of the expected phenomenon is - 11,46		

This correlation relationship is statistically significant due to the fact that the χ^2 criterion with the Yates correction is larger in comparison with the critical point

of the Pearson distribution χ^2 7.975> 6.6349 with degree of freedom 1 (p <0.01).

Table 4. Criteria for assessing the relationship between risk factor and the result of the presence / absence (palliative) of anti-tubercular treatment and body weight deficit.

Name of the criterion	Value of the criterion	The level of significance
Criterion φ Criterion *V* Cramer The criterion for Chuprova is	0,340	average
Coefficient of conjugacy of Pearson (C) is	0,322	average
The normalized Pearson coefficient (C ') of	0,455	relatively strong

Note: interpretation of the obtained values of statistical criteria was performed in accordance with the recommendations of Rea & Parker

The results of calculating Pyrson's χ^2 criterion of the dependence of the risk factor between levels of TNF-α in the blood and weight deficit are shown in Table 5-7.

Table 5. The calculation of the odds ratio with a 95% confidence interval in the TNF-α conjugation table and body weight deficit.

	Risk Factor (TNF-α) increased	Risk Factor (TNF-α) in normal	Together
Deficiency of body weight available (BMI<18.5 kg/m^2)	29	3	32

Deficiency of body weight is absent (BMI≥18.5 kg/m^2)	7	42	49
Together	36	45	81

The chance to find a risk factor in the main group is 9,667. The chance to find a risk factor in the control group is 0.167. The odds ratio (OR) is 58,000. Standard error relationship chance (S) is 0.731. Lower limit 95% confidence interval (CI) is 13.839. Upper limit 95% confidence interval (CI) is 243,074. At confidence intervals, 95% of the statistics can be considered reliable ($p < 0,05$).

Table 6. Criteria for assessing the significance of differences in outcome depending on the effect of TNF-α risk factor and body weight deficit.

Name of the criterion	Value of the criterion	The level of significance
Criterion χ^2	45,689	$p<0,01$
Criterion χ^2 with Yeats correction	42,650	$p<0,01$
Criterion χ^2 corrected for probability	51,184	$p<0,01$
Fischer's exact criterion (two way)	0,0000	$p<0,05$
The minimum value of the expected phenomenon is - 14,22		

This correlation relationship is statistically significant because the χ^2 criterion with the Yates correction is larger in comparison with the critical point of the Pearson distribution χ^2 42,650> 6,6349 with degree of freedom 1 ($p < 0,01$).

Table 7. Criteria for assessing the relationship between risk factor and TNF-α and body weight deficit.

Name of the criterion	Value of the criterion	The level of significance
Criterion φ Criterion *V* Cramer The Chuprova criterion	0,751	strong
Pearson coefficient of conjugacy (C)	0,601	strong
The normalized Pearson coefficient (C ')	0,849	very strong

Note: interpretation of the obtained values of statistical criteria is in accordance with the recommendations of Rea & Parker [].

CONCLUSIONS

1. Thus, the chance for a group of patients with TNF-α in the bloodstream above the norm and with a deficit of weight (BMI <18.5) is 58.0 times higher than in patients with normal weight and normal TNF-α levels in blood.

2. The chance in the group of patients receiving palliative care to detect body weight deficiency (BMI <18.5 kg/m^2) is 5,184 times higher than in patients receiving anti-TB treatment in category 4.

3. According to the calculation, the value of the Pearson correlation coefficient was 0.455, which corresponds to the relatively strong correlation between the presence / absence of PTP therapy and weight deficit.

4. According to the calculation, the value of the Pearson correlation coefficient was 0.849, which corresponds to a very strong TNF-α binding affinity and weight deficit.

5. There is a correlation between the presence or absence of antimycobacterial treatment in patients with chemoravier tuberculosis and the presence of weight deficit and TNF-α ($p < 0.05$). Data on high risk factors for the development of weight deficit and TNF-α in patients with chemo-resistant tuberculosis who receive palliative treatment compared with patients receiving anti-TB treatment are available.

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