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Immunoprevention of contact children from focies of chemoresistant tuberculosis infection with BIVEL immunomodulator (BI-V)

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Aim – to study the feasibility of using the natural immunomodulator BIVEL (BI-V) as a non-specific immunoprevention of tuberculosis (TB) among contact children from focies of multidrug-resistant tuberculosis infection (FsMDR-TBI) on the basis of clinical and immunological studies.

Materials and methods. The object of study: 120 contacted from FsMDR-TBI (75 children and 45 adolescents). The Group 1 – 95 children/adolescents who did not receive BI-V and the Group 2 – 25 patients who received BI-V. The state of phagocytic reactivity of immunity; cellular and humoral immunity; interleukins and specific immunity were determined. Statistical analysis of the obtained results was performed based on a software package Excel.

Results. In infected children/adolescents with FsMDR-TBI, insignificant functional disorders of the cellular response were revealed (decrease by 1.3 times IRI CD3+CD4+/CD3+CD8+), a shift in the balance in the regulatory system towards pro-inflammatory cytokines (increase by 2.0 times TNF-α/IL-10). The existing deviations in the regulatory and cellular response systems disappeared after the completion of the autumn-spring BI-V course. Preventive administration of immunomodulator BI-V to infected children/adolescents with FsMDR-TBI reduced the frequency of acute respiratory viral infections and exacerbations of bronchopulmonary diseases by 2.0 times, the development of latent tuberculosis infection into an active process by 2.6 times. Among children of the Group 2 – 8% of people fell ill with various forms of primary pulmonary TB, among children of the Group 1 – 22.1%. In both groups, the maximum level of TB occurred in the first two years of observation.

Conclusions. The introduction of the algorithm of preventive measures with appointment of BI-V confirmed feasibility of using this immunomodulator for contact children/adolescents with FsMDR-TBI.

The study was carried out in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethical Committee of the participating institution. The informed consent of patient was obtained for conducting the studies.

No conflict of interests was declared by the authors.

Keywords: immunoprevention, contact children and adolescents, focies of multidrug-resistant tuberculosis.

Імунопрофілактика контактних дітей з осередків хіміорезистентної туберкульозної інфекції імуномодулятором BIVEL (BІ-V)

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Мета – обґрунтувати доцільність застосування неспецифічного імуномодулятора Bivel (BI-V) у ролі неспецифічної імунопрофілактики туберкульозу (ТБ) у контактних дітей з осередків множинної лікарсько-стійкої туберкульозної інфекції (ОМЛС-ТБІ) на підставі клініко-імунологічних досліджень.

Матеріали та методи. Об'єкт вивчення: 120 контактних з ОМЛС-ТБІ (75 дітей та 45 підлітків). Перша група – 95 дітей/підлітків, які не отримували Bi-V, друга – 25 інфікованих дітей/підлітків, які отримали BI-V. Визначено фагоцитарну ланку імунітету; клітинного та гуморального імунітету; інтерлейкінів та специфічного імунітету. Статистичний аналіз отриманих результатів виконано на підставі пакета програм у системі Excel.

Результати. В інфікованих дітей/підлітків з ОМЛС-ТБІ виявлено незначні функціональні порушення клітинної відповіді (зменшення в 1,3 раза IPI CD3+CD4+/CD3+CD8+, $p<0,05$), зміщення балансу в регуляторній системі в бік прозапальних цитокінів (зростання у 2,0 рази TNF-α/IL-10, $p<0,01$). Наявні відхилення в регуляторній системі та системі клітинної відповіді зникали після завершення осінньо-весняного курсу BI-V. Призначення з профілактичною метою імуномодулятора BI-V інфікованим дітям/підліткам з ОМЛС-ТБІ зменшило у 2,0 раза частоту гострих респіраторних вірусних інфекцій та загострень бронхо-легеневих захворювань, у 2,6 раза переростання латентної туберкульозної інфекції в активний процес. На різні форми первинного ТБ легень захворіло 8% осіб другої групи, і 22,1% – першої, $p<0,05$. В обох групах максимальний пік захворювання припав на перші два роки спостереження.

Висновки. Упровадження алгоритму профілактичних заходів із призначенням Bi-V підтвердило доцільність застосування цього імуномодулятора контактним дітям/підліткам з ОМЛС-ТБІ.

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом зазначеної в роботі установи. На проведення досліджень отримано інформовану згоду батьків дітей.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: імунопрофілактика, контактні діти та підлітки, осередки мультирезистентного туберкульозу.

One of the most important problems of modern medicine is tuberculosis (TB). It has a direct impact on the socio-economic indicators of the development of society, connection with the increasing number of newly diagnosed patients with a specific process, which is due to resistant strains of Mycobacterium TB (MBT) to Antimycobacterial Drugs (Anti-TBDs) [7,8,10–12,14,17].

The greatest attention is required by children and adolescents from the focies of multidrug-resistant tuberculosis infection [4,6] in the context of an increase in morbidity among the adult population to resistant forms of pulmonary TB (PTB). In particular, preventive measures are aimed at preventing the development of a dangerous disease [2,8,9]. The main place among them belongs to the specific prevention and chemoprevention (CP) of TB [3,5,15,16,18].

TB belongs to a group of diseases characterized by manifestations of chronic granulomatous inflammation of the immune genesis due to a long-lasting reaction to the persistent causative agent of TB into organs and tissues [13]. Immunocompetent cells are the main participants of anti-TB protection, forming a specific granuloma, which is primarily an insulator of the infectious agent and a consequence of its action. An important role both in determining the etiology of the process and in establishing the features of the course and its prognosis have immunological diagnostic methods, both in adults and children/adolescents [2,9,16].

To date, the CP of TB includes the administration of isoniazid, or isoniazid and rifampicin to children and adolescents with first-time positive reactions to tuberculin(«conversion»); children and adolescents with hyperergic reactions to tuberculin (17 mm or more); children and adolescents (uninfected) from focies of tuberculosis infection (TBI) during the most unfavorable periods of contact with bacterial excretors according to regulatory documents. However, such CP is prescribed to contact children living in focies of sensitive TBI [15]. If the child is from the focies of multidrug-resistant TBI, it is not advisable to prescribe the first (I) line Anti-TBDs [12]. In such cases, the choice of Anti-TBDs for CP is carried out taking into account the source of TBI with children/adolescents were in contact. In this case, contact children and adolescents often have problems when prescribing a second (II) line Anti-TBDs for CP. In this regard, a search is underway for Anti-TBDs that could be used for CP, children/adolescents who have been in contact with a patient with multidrug-resistant pulmonary tuberculosis (MDR-PTB).

Researches by R.M. Daly et al. [5] indicate that vitamin D deficiency in winter and spring is 3–4 times higher than in summer, and twice as high in people living in latitudes 35° parallels. A. Fares [7] believes that important reasons that can affect the seasonality of diseases are the variability of vitamin D levels, seasonal changes in the immune system, seasonal changes in nutrition, etc., analyzing 12 studies for the period from 1971–2006 in 11 countries. Respiratory diseases are more often detected in winter, but TB is not associated with seasonality. Although according to researches by L.I. Mykolyshyn, Z.I. Piskur [13], J.H. MacLachlan [10], C.M. Parrinello [14], T. Wingfield, et al. [18], susceptibility to TB may be caused by low levels of vitamin D. L.I. Mykolyshyn and Z.I. Piskur [13] note that 71.1% of children with TB of the respiratory system experienced a deficiency of vitamin D, 21.1% – had its insufficiency, and only 7.8% of children had normal vitamin D level. Therefore, based on the considerations of reducing the body's immune reactivity, vitamin D deficiency (not only seasonal but also alimentary, which is often available in childhood) we chose BIVEL (BI-V).

Aim – to study the feasibility of using the natural immunomodulator BI-V as a non-specific immunoprevention of TB among contact children from the focies of multidrug-resistant TBI (FsMDR-TBI) on the basis of clinical and immunological studies.

Materials and methods of the study

The object of our study was 120 contacts from FsMDR-TBI, including 75 children and 45 adolescents: 75 (62.5%) children aged 0 to 14 years and 45 (37.5%) teenagers aged 15 to 18 years. The contacted children underwent clinical, X-ray, and laboratory examinations. Children and adolescents from FsMDR-TBI were divided into two groups: Group 1 – 95 people, who did not receive BI-V; Group 2 included 25 infected children/adolescents who were prescribed BI-V, of which 10 people – with hyperergic reaction, 15 people – with «conversion» of the tuberculin reaction. Immunomodulator BI-V was prescribed according to the instructions. The course of non-specific immunoprevention was repeated twice a year (spring and autumn) in the most threatening periods for the occurrence of the disease.

Adults (source of TBI) underwent microbiological examinations: detection of MBT in sputum by

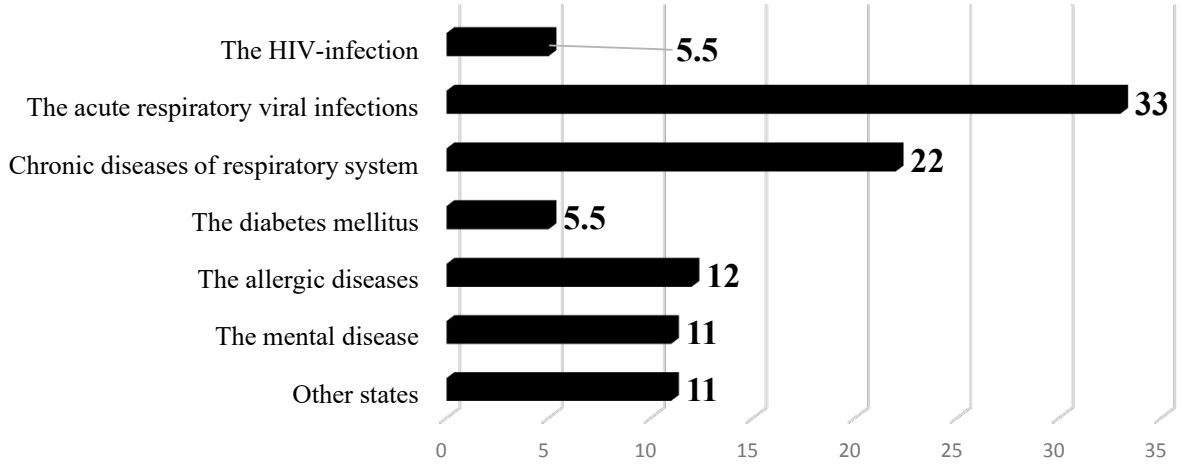

Fig. 1. Frequency of medical risk factors for TB in children/adolescents from FsMDR-TBI, %

smear microscopy, inoculation of material on Lowenstein–Jensen medium, typing of isolated MBT on BACTEC MGIT 960, determination of drug susceptibility test (DST) MBT strains to I and II line Anti-TBDs, molecular genetic sputum examination. Molecular genetic examinations included: GeneXpert MBT/RIF and linear probe analysis, determining the sensitivity of MBT to Anti-TBDs I (HR) using GenoType MTBDRplus hybridization kits and II line (to fluoroquinolones and aminoglycosides) using the MTBDRsl GenoType hybridization kit [1].

The study of the state of the body's immunological reactivity in patients with PTB remains relevant to determine the degree of activity of the specific process, diagnosing, and differential diagnosing of pulmonary pathology [16]. Determination of the population and subpopulation composition of blood lymphocytes (CD3+, CD3+CD56+, CD3+HLA-DR+, CD3+CD4+, CD4+45RA+, CD3+CD8+, CD4+/CD8+, CD19+, CD16/56+, CD16/56+CD8+) was carried out in 25 children before and in 22 children after immunoprevention in contact from FsMDR-TBI, in the medical laboratory «DELA» by direct immunofluorescence method using anti-CD monoclonal antibodies with subsequent identification of the surface structures of lymphocytes on the flow cytofluorimeter FACScan BD Bioscience, USA.

B-cell function was evaluated by serum immunoglobulin (Ig) levels of types A, M, G, which were determined by solid-phase enzyme immunoassay using HEMA-MEDICA test systems (Ukraine) and by counting the results on a spectrophotometry analyzer – μ Quant (BioTek, USA), measuring range: 200–999 nm, error ±1.0%.

The concentration of circulating immune complexes was determined by precipitation in polyethylene glycol using HEMA-MEDICA test systems (Ukraine) and taking into account the results on the μQuant spectrophotometer (BioTek, USA), the measurement range: 200–999 nm, error±1.0%.

The levels of cytokines IL-1β, IL-2, IL-10, and tumor necrosis factor α (TNF-α) in the blood serum were determined using Vector-Best enzyme immunoassay kits (MR-96A analyzer).

We chose a direction to strengthen immunity by using an immunomodulator BI-V to improve the method of non-specific immunoprevention of TB in contact children and adolescents from FsMDR-TBI. This is a combination drug and includes dry fermentate Saccharomyces cerevisiae (EpiCor®), vitamin C, zinc (Zn) vitamin D_3. The suspension is available in 120 ml for internal (*per os*) use. The manufacturer is ErgoPharma Ltd (Slovenia). The immunomodulator BI-V was prescribed twice a year (in autumn and spring) for children over 3 years old at 5.0 ml once a day for 24 days.

For statistical analysis of the raw data, the software for mathematical calculations, their graphic representation, and analysis results in Excel with the Microsoft Office application package were used. Statistical processing of the research results was performed using the methods of parametric (variational) statistics in compliance with the conditions for estimating the type of distribution. The results are presented in the form of the average statistical value of the indicator and the error of the average M±m. The probability of the obtained results was evaluated using the Student's criterion and Mann–Whitney. A p-value < 0.05 was considered statistically

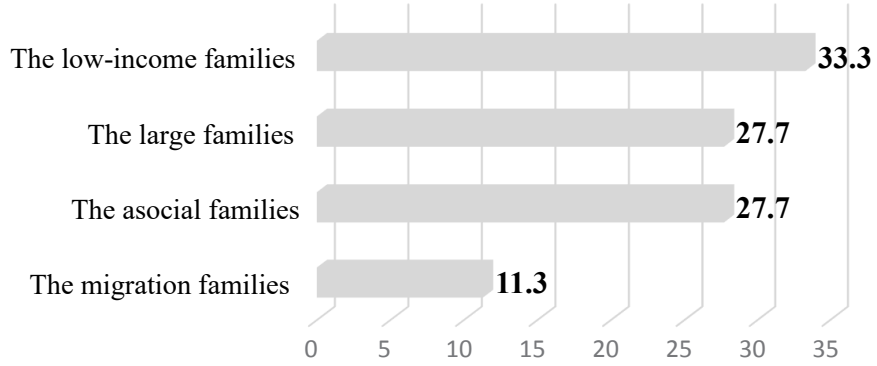

Fig. 2. Frequency of social risk factors for TB in contacted children/adolescents from FsMDR-TBI, %

significant. For statistical processing of the material, the STATISTICA 2006 computer software package was used.

The study was carried out in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethical Committee of the participating institution. The informed consent of the patient was obtained for conducting the studies.

Results of the study and discussion

All contact people had a history of risk factors for developing TB. Adults with drug-resistant PTB exposed isolated MBT with the following resistance profile: multi-resistant MBT strains isolated 11 (22.0%), rifampicin resistance (Rif-TB) – 23 (46.0%), pre-extremal drug resistance (preEx-DR-TB) – 5 (10.0%), extremal drug resistance (Ex-DR-TB) – 11 (22.0%). 30.0% of adults (source of TBI) died, which is connected to the progression of a specific process from FsMDR-TBI. Most of the contact children/adolescents who became ill with PTB from FsMDR-TBI had concomitant diseases: acute respiratory viral infections (ARVI) – 33.0%, chronic non-specific diseases of the respiratory system – 22.0% and other pathologies (convulsions, mental and allergic diseases, diabetes mellitus), which contributed to a decrease in body's reactivity (Fig. 1).

Important impact on the development of TB in children and adolescents from FsMDR-TBI had social factors (Fig. 2).

Our studies have shown that children/adolescents from low-income (33.0%), large (27.7%), asocial (27.7%), and migrant families (11.3%), the number of which increased during the war, were most often in contact with TB.

Thus, TB disease among children from contact groups is closely related to medical and social factors that lead to a decrease in the body's protective reactions and contribute to the development of specific inflammation.

The protective level of the immune system may be insufficient also for several other reasons. It depends on the nature of the antigenic effect, the type of pathogen, its virulence, and massiveness, on the state of the macroorganism, which is influenced by factors of the external and internal environment (the state of the nervous and endocrine systems, the nature of metabolic processes), on the presence of primary or secondary immunodeficiencies, etc. Therefore, work in focies of TBI is quite important: identification of infected individuals, including those with suppressed immune status, CP, determination of the need for immunotherapy, and control over their effectiveness. Selected and carried out preventive measures should work to prevent the development of the disease.

An important stage of work in the focus of any infection is the identification of infected people. The intradermal tuberculin Mantoux test with 2 TU PPD-L is the most common and inexpensive method for detecting MBT infection. Recently, QuantiFERON-TB Gold ELISA (Quantiferon test) has been used in Ukraine for in vitro diagnostics. It is an enzyme-linked immunosorbent method for detecting cellular response to peptide antigens ESAT-6 and SFR-10 by interferon levels in the blood. In our study, the detection of infected children/adolescents from contacts was carried out in parallel: Mantoux test with 2 TU PPD-L and QuantiFERON-TB tests.

The results of the studies showed that the presence of tuberculin allergy was ascertained in 82.5% (99) children based on the Mantoux test. In 33.3% (40) cases of the total number of examined (120 children), the tuberculin reaction was slightly positive, the papule diameter was up 5 mm to 11 mm. 49.2%

Table 1

Tuberculin sensitivity among children/ adolescents from FsMDR-TBI

Size of papule, mm	Researched groups (n=120)	
	abs.	%
0–4	21	17.5
5–11	40	33.3
12–16	30	25.0
17 and more	29	24.2
Average size of papules, mm	15.4±0.3	

(59) of children/adolescents had intense and hyperergic tuberculin tests (Table 1). The «conversion» of the tuberculin Mantoux test with 2 TU PPD-L was noted in 40 (33.3%) children.

The Quantiferon test was given to children from a boarding school where a nurse contracted active TB. The presence of latent tuberculosis infection (LTBI) was confirmed in 94.0% of contact children. In 6.0% of children, the Quantiferon test was negative. Two children fell ill with TB of the intrathoracic lymph nodes (ITLNs).

Therefore, according to the results of specific diagnostic tests, on average 84% of children and adolescents from FsMDR-TBI had LTBI. LTBI confirmed by Mantoux reaction with 2 TU PPD-L in 82.5%, using QuantiFERON-TB test – in 86.7% of children.

Identification of persons with LTBI in the focies of TBI excludes the possibility of carrying out unreasonable chemopreventive measures. However, according to a number of indicators of clinical and laboratory examinations, they can be considered without LTBI. In accordance with the clinical module [12] for CP it is recommended to prescribe levofloxacin (Lfx) and protionamide (Pto) to contact children from FsMDR-TBI. However, Lfx causes many side effects: nausea, vomiting, diarrhea, hyperbilirubinemia, skin rashes, itching, headache, fatigue, sleep disorders, hallucinations, inhibition, dizziness, psychosis, leukopenia, agranulocytosis, thrombocytopenia, nephrotic syndrome, sometimes acute renal failure, swelling of the face, vocal cords; arthralgia, myalgia, visual impairment, photosensitization, etc. Side effects of Pto can be: stomatitis, a feeling of metallic taste in the mouth, nausea, vomiting, diarrhea, impaired liver function, anorexia, neuritis, headache, weakness, poor sleep, neurosis, depression, tachycardia, arterial hypotension.

In practice, CP of MDR-TB among contact children and adolescents has not been widely used due to the high toxicity of Lfx and Pto. Always patients refuse to take these drugs or the timing of CP is violated, which reduces its effectiveness. One of the solutions to this problem is the use of additional pathogenetic preparations to reduce the side effects of Anti-TBDs or in case of complete failure – the search for an alternative way to control infection (strengthen immunity by using immunomodulatory preparations) [9].

The winter and spring months are when seasonal colds are at their highest. People experience vitamin D deficiency during this period.

In the cold months of the year, the frequency of ARVI, and relapses of non-specific bronchopulmonary diseases increases sharply, which weakens the immune protection. Therefore, one of the factors in strengthening the body's resistance and reducing the risk of developing TB will be the prevention of colds among contact people.

Our research showed that in the Group 1 of children who did not receive BI-V, the frequency of ARVI was 55.5%, and relapses of non-specific bronchopulmonary diseases – 33.3%. Administration of the immunomodulator BI-V significantly reduced the frequency of these diseases to 27.8% and 16.7%, respectively, $p<0.05$. The children's appetite, memory improved, and physical activity increased. They became more successful in their studies.

An assessment of immune status with the examination of the cellular immune response system, pro- and anti-inflammatory cytokines in children/adolescents of the Group 2 was carried out. In infected children/adolescents from FsMDR-TBI, deviations in the system of cellular protection are associated with quantitative changes (decrease/increase) of the number of certain lymphocytic levels, a loss of balance in the system of intercellular cooperation between individual pools of lymphocytic cells, and the appearance of an imbalance in the regulatory system of pro- and anti-inflammatory cytokines. This is confirmed by the results of researches on cell populations: common T-lymphocytes CD3+, T-helper lymphocytes CD3+CD4+, T-suppressor/ cytotoxic CD3+CD8+. In infected children/adolescents from FsMDR-TBI, only trends to a slight decrease in the number of CD3+ (relative to donors, $p>0.05$), CD3+CD4+ ($p>0.05$), the increase of T-CD3+CD8+ ($p>0.05$) were noted. The indicators of which were not included the confidence interval of the norm and did not give a clear picture of the course of immune reactions in children with LTBI

Table 2

Features of immune response in contact children/adolescents from FsMDR-TBI before and after preventive BI-V course

Indicators	Researched groups		
	Donors (n=17)	Contact children/adolescents	
		before prevention (n=25)	after prevention (n=22)
T- lymphocytes CD3+ (%)	69.5±2.0	63.8±3.1	73.6±3.3#
T- helper lymphocytes CD3+CD4+ (%)	39.0±1.6	34.2±2.7	38.3±2.4
T- suppressor/cytotoxic CD3+CD8+ (%)	28.5±1.4	33.5±2.3	29.1±1.8
Ratio CD3+CD4+/ CD3+CD8+ (IRI Tx/Tc)	1.30±0.08	1.02±0.10*	1.32±0.10#
TNF-α pg/ml	1.47±0.12	3.50±0.32*	2.13±0.28*#
IL-6 pg/ml	1.72±0.14	2.25±0.20*	1.84±0.16#
IL-10 pg/ml	5.14±0.26	5.23±0.42	5.30±0.29
TNF-α/IL-10	0.33±0.07	0.67±0.05*	0.40±0.08#
IL-6/IL-10	0.29±0.05	0.43±0.07	0.35±0.04

Notes: * – the difference is significantly up to the donor group, p<0.05; # – the difference is significant before the start of the preventive BI-V course, p<0.05.

are presented in Table 2. In practice, the immunoregulatory indexes are often used which describe the ratio of different subpopulations of lymphocytic cells and characterize the direction of the immune response. The most commonly used is the immunoregulatory index (IRI) CD4+/CD8+. It evaluates the imbalance between regulatory T-helpers and T-suppressor-cytoxic lymphocytes and characterizes the immunoregulatory phase of the immune response of the inflammatory, allergic, or combined types.

In infected children/adolescents from FsMDR-TBI, the ratio of CD3+CD4+ to CD3+CD8+ corresponded to the index (1.02±0.10) relative to (1.30±0.08) in healthy individuals (p<0.05). The difference was significant and indicated a shift in equilibrium towards suppressor-cytotoxic reactions of the immune response of the inflammatory type.

Examination of children/adolescents after a course of preventive measures with BI-V indicated an increase of 1.2 times (relative to the initial values) of total T-lymphocytes CD3+ (p<0.05), restoration of the balance between the lymphocyte pools of CD3+CD4+ and CD3+CD8+, the normalization of the IRI (p<0.05).

The presence of LTBI in children/adolescents from FsMDR-TBI was indicated by an increase in the content of pro-inflammatory interleukins in the blood: TNF-α (relative to donors, p<0.05), IL-6 (p<0.05) and the cytokine index TNF-α/IL-10 (p<0.05). The cytokine index TNF-α/IL-10 outlined the dominance of pro-inflammatory mediators.

In the regulatory system of the immune response, a decrease in the content of pro-inflammatory cytokines was noted: by 1.6 times TNF-α – from (3.50±0.32) pg/ml to (2.13±0.28) pg/ml (p<0.05) with the norm of (1.47±0.12) pg/ml (p<0.05); 1.2 times IL-6 – from (2.25±0.20) pg/ml to (1.84±0.16) pg/ml (p<0.05) with the norm of (1.72±0.14) pg/ml (p>0.05); 1.7 times cytokine index TNF-α/IL-10 – from (0.67±0.05) pg/ml to (0.40±0.08) pg/ml (p<0.05) with the norm of (0.33±0.07) pg/ml (p>0.05) after completion of the preventive BI-V course.

Consequently, infected children/adolescents from FsMDR-TBI had minor functional disorders of the immune response mechanisms. Disorders of immunoregulatory reactions were revealed, due to a shift in the immune response towards suppressor-cytotoxic reactions, and the presence of an imbalance in the regulatory system of pro- and anti-inflammatory cytokines with the activation of the production of pro-inflammatory cytokines. The existing abnormalities in the regulatory system of the immune response disappear after the completion of the autumn-spring preventive BI-V course.

Assessment of the activity of the specific process, and the effectiveness of preventive or treatment measures of TB requires repeated specific tests, including a tuberculin test with 2 TU PPD-L. Reducing the sensitivity of the skin to tuberculin is one of the indicators of the success of these measures. 15 children/adolescents had LTBI and 10 people – with hyperergic reactions who preventively took BI-V. As a result of the autumn-spring BI-V course, a decrease in skin sensitivity to tuberculin was observed. The intensity of the Mantoux test with 2 TU PPD-L among children with LTBI decreased up (12.2±0.4) mm to (10.7±0.5) mm, p<0.05, among people with hyperergic reaction – up (18.6±1.0) mm to (14.2±0.7) mm, p<0.01 (Table 3).

Table 3

Dynamics of Mantoux test results with 2 TU PPD-L before and after preventive measures in contact children from FsMDR-TBI

Groups	Size of papule, mm	
	before prevention	after prevention
LTBI (n=15)	12.2±0.4	10.7±0.5*
Hyperergic reaction (n=10)	18.6±1.0	14.2±0.7*

Note: * – difference is significantly in relation to the parameters before the BI-V prevention, p<0.05–0.01.

Table 4

TB in children/adolescents from FsMDR-TBI during 4 years observation

Years of observation	Group 1 (n=95)		Group 2 (n=25)		p
	abs.	%	abs.	%	
For 4 years	21	22.1	2	8	<0.05
The first year	8	38.2	1	50	>0.05
The second year	9	42.8	1	50	>0.05
The third year	2	9.5	-	-	>0.05
The fourth year	2	9.5	-	-	>0.05

Note: * – the difference is significantly up to the parameters of the first group, p<0.05.

The generalization of 4-year observations of contact children/adolescents from FsMDR-TBI regarding the development of an active specific process in them was the most important final stage of the studies.

The distribution of TB indicators during 4 years of observations is presented in Table 4.

A four-year observation of children/adolescents from FsMDR-TBI showed the maximum level of TB disease in the first two years of observation. In the first year, the active process was diagnosed in 38.2% (8 cases) children of the Group 1 and 50.0% (1 case) children of the Group 2. In the second year – 42.8% (9 cases) and 50.0% (1 case), respectively. In subsequent years, among the contacts who did not receive BI-V another 19.0% (4 cases) of people fell ill: 9.5% (2 cases) of children in the third year and 9.5% (2 cases) in the fourth year of observation.

Consequently, 22.1% (21 cases) of contacts who did not receive the non-specific immunomodulator BI-V (Group 1) fell ill with various forms of primary PTB, at the same time in the Group 2 – 8.0% (2 cases), p<0.05.

Conclusions

1. In infected children/adolescents from FsMDR-TBI insignificant functional disorders of the cell response were revealed at the level of immunoregulatory processes due to the dominance of suppressor-cytotoxic reactions (decrease by 1.3 times IRI CD3+CD4+/CD3+CD8+, p<0.05, relative to donors), a shift in balance in the regulatory system of pro- and anti-inflammatory cytokines towards pro-inflammatory cytokines (increase by 2.0 times TNF-α/IL-10, p<0.01, relative to normal). The existing deviations in the regulatory system and the cellular response system disappeared after the completion of the autumn-spring BI-V course.

2. The preventive administration of the immunomodulator BI-V to infected children/adolescents from FsMDR-TBI reduced the frequency of ARVI and relapses of non-specific bronchopulmonary diseases by 2.0 times, the development of LTBI into an active process by 2.6 times, improved appetite, memory, academic performance, and increased physical activity.

3. Among children from FsMDR-TBI who took a preventive BI-V course, 8% of people fell ill with various forms of primary PTB, among the children who was not prescribed the BI-V – 22.1%, p<0.05 during the 4-year of observation. The maximum level of TB occurred in the first two years of observation in both groups.

4. The non-specific immunomodulator BI-V is an effective drug for the prevention of MDR-TB among contact children/adolescents from FsMDR-TBI. In children who were treated with BI-V, LTBI was 2.8 times less likely to transform the active process than in those infected who did not take this drug.

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