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The feasibility of immunocorrective therapy in the treatment of children with new tuberculosis cases

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Key words:
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Aim. To substantiate the expediency of the immunocorrective therapy use in combined treatment by studying the effectiveness of the immunomodulator azoximer bromide aimed at correcting the immunological changes in children with new tuberculosis (TB) cases.

Materials and methods. The study on the effectiveness of immunocorrective therapy in the complex treatment of children with new TB cases was conducted at the beginning of antimycobacterial therapy (AMBT) and at the end of the maintenance phase (MF) of AMBT. For this purpose, 51 children with new TB cases and immunologic changes were included in the study and divided into 2 groups: 26 children received immunomodulator azoximer bromide in the combined therapy on the background of AMBT (main group) and 25 children were assigned to receive only AMBT (control group). The groups were identical in age, sex, prescribed AMBT regimens, and severity of the specific process. The children from the main group along with the standard AMBT additionally used azoximer bromide (immunomodulator) to correct immunological changes: for children under 10 years of age – 6 mg twice a day, for children over 10 years – 12 mg twice a day; the treatment course – 14 days. The study results were processed on a personal computer using the statistical package of the licensed program Statistica, version 13 (Copyright 1984–2018 TIBCO Software Inc. All rights reserved, License No. JPZ804I382130ARCN10-J).

Results. Given the results obtained, the use of immunomodulator azoximer bromide in the complex treatment for children with new TB cases, alongside normalization of all cytokine profile indicators and the balance in the regulatory system of pro- and anti-inflammatory cytokines, helped to achieve by the end of treatment: a shorter average time to culture conversion by 0.9 (1.5 (1.0; 2.0) months against 2.4 (2.0; 3.0) months; $P < 0.01$), positive radiological dynamics of 77 % ($\chi^2 = 5.79$; $P < 0.01$), reduced time of destruction healing by 2.1 (1.7 (1.0; 2.0) months against 3.8 (3.0; 4.0) months, $P < 0.02$), shorter average time of the basic AMBT course by 1.5 (6.2 (5.6; 6.8) months against 7.7 (6.0; 9.3) months; $P < 0.01$). Combined treatment tolerability was satisfactory in all 100 % of cases.

Conclusions. Immunomodulator azoximer bromide as a part of the combined therapy for children with new TB cases can not only restore the body immune reactivity, but also reduce the specific process activity on the background of AMBT, shorten the average time to culture conversion by 0.9 months and destruction healing by 2.1 months, reduce the average duration of the main AMBT course by 1.5 months. In addition, this approach to therapy helps to conduct standard AMBT without changing the treatment regimen.

Ключові слова:
діти, туберкульоз, комплексне лікування.

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Доцільність застосування імунокоригувальної терапії в комплексному лікуванні дітей із новими випадками захворювання на туберкульоз

Ю. В. Мирончук, О. М. Разнатовська

Мета роботи – обґрунтувати доцільність застосування імунокоригувальної терапії в комплексному лікуванні шляхом вивчення ефективності імуномодулятора азоксимеру броміду, спрямованого на корекцію імунологічних змін у дітей із новими випадками захворювання на туберкульоз (ТБ).

Матеріали та методи. Вивчення ефективності застосування імунокоригувальної терапії в комплексному лікуванні дітей із новими випадками захворювання на ТБ здійснили на початку антимікобактеріальної терапії (АМБТ) та після завершення підтримувальної фази (ПФ) АМБТ. Для цього у дослідження залучили 51 дитину з новими випадками захворювання на ТБ з імунологічними змінами. Пацієнтів поділили на 2 групи: 26 хворих, які в комплексному лікуванні на тлі АМБТ отримували імуномодулятор азоксимеру бромід (основна група), та 25 дітей, які одержували тільки АМБТ (контрольна група). Групи зіставні за віком, статтю пацієнтів, за призначеними режимами АМБТ і тяжкістю специфічного процесу. В дітей основної групи на тлі стандартної АМБТ для корекції імунологічних змін додатково застосовували азоксимеру бромід (імуномодулятор): у хворих віком до 10 років – внутрішньо по 6 мг двічі на добу, понад 10 років – по 12 мг двічі на добу; курс лікування – 14 діб. Результати дослідження опрацювали, застосувавши статистичний пакет ліцензійної програми Statistica, версія 13 (Copyright 1984–2018 TIBCO Software Inc. All rights reserved. Ліцензія № JPZ804I382130ARCN10-J).

Результати. Виявили, що в дітей із новими випадками захворювання на ТБ застосування імуномодулятора азоксимеру броміду в комплексному лікуванні на тлі нормалізації всіх показників цитокінового профілю та досягнення балансу в регуляторній системі про- до протизапальних цитокінів сприяє скороченню середніх термінів припинення бактерієвиділення на 0,9 місяця (1,5 (1,0; 2,0) місяця проти 2,4 (2,0; 3,0) місяця; $p < 0,01$), досягненню позитивної рентгенологічної динаміки у 77 % випадків ($\chi^2 = 5,79$; $p < 0,01$), скороченню термінів загоєння деструкцій на 2,1 місяця (1,7 (1,0; 2,0) місяця проти 3,8 (3,0; 4,0) місяця; $p < 0,02$) та середніх термінів основного курсу АМБТ на 1,5 місяця (6,2 (5,6; 6,8) місяця проти 7,7 (6,0; 9,3) місяця; $p < 0,01$). Переносність комплексного лікування у всіх випадках задовільна.

Висновки. Додавання імуномодулятора азоксимеру броміду в комплексну терапію дітей із новими випадками захворювання на ТБ дає змогу не лише відновити імунологічну реактивність організму, але й зменшити активність специфічного процесу на тлі АМБТ, скоротити середні терміни припинення бактерієвиділення на 0,9 місяця та терміни загоєння деструкцій на 2,1 місяця, скоротити середні терміни основного курсу АМБТ на 1,5 місяця. Такий підхід до лікування дає змогу призначати стандартну АМБТ без зміни режиму.

International standards and recommendations [5–7,9,10], national standards and treatment protocols [13,14] for children with tuberculosis (TB) are based on the use of only antimycobacterial therapy (AMBT) and do not provide immunocorrective therapy for immunological abnormalities. AMBT does not stimulate the body defenses and can not provide complete recovery in all cases. In most patients, the basic indicators of immunity normalizes in process of effective treatment, but some patients develop a secondary immunodeficiency state [11,12,15], which gives of the feasibility of the following studies aiming to use immunocorrective therapy in children with new TB cases.

The drug azoximer bromide is an immunomodulator [4]. It increases the ability of phagocytes to absorb and kill microbial bodies without affecting the normal performance of the immune system by activating the monocyte-macrophage system.

Aim

To substantiate the expediency of the use of immunocorrective therapy in combined treatment by studying the effectiveness of immunomodulator azoximer bromide aimed at correcting the immunological changes of children with new TB cases.

Materials and methods

The study on the effectiveness of immunocorrective therapy in the complex treatment of children with new TB cases was conducted at the beginning of AMBT and at the end of the maintenance phase (MF) of AMBT.

The study on the effectiveness of immunocorrective therapy in the complex treatment of children with new TB cases was conducted at the beginning of AMBT and at the end of the AMBT MF. For this purpose, 51 children with new TB cases and immunologic changes were included in the study and divided into 2 groups: 26 children received immunomodulator azoximer bromide in the combined therapy on the background of AMBT (main group) and 25 children were assigned to receive only AMBT (control group). The groups were identical in age, sex, prescribed AMBT regimens, and the specific process severity. All children with new TB cases included in the study were treated in the Children's Department of the Municipal Non-Profit Enterprise "Zaporizhzhia Regional Clinical and Diagnostic Center of Phthisiatry and Pulmonology" of Zaporizhzhia Regional Council.

The children from the main group on the background of standard AMBT additionally used azoximer bromide (immunomodulator) to correct immunological changes: for children under 10 years of age – 6 mg twice a day, for children over 10 years – 12 mg twice a day; treatment course – 14 days.

The effectiveness of immunomodulator azoximer bromide in the combined treatment of children with new TB cases was evaluated according to the following indicators:

– smear/culture conversion;

– resorption of focal and infiltrative changes in the lungs according to chest X-ray examination;

– destruction in the lungs (recovery, regression, progression, without changes) according to chest X-ray and the average time of destruction healing;

– satisfactory AMBT tolerability;

– disappearance of clinical symptoms;

– normalization of cytokine profile.

The study results were processed on a personal computer using the statistical package of the licensed program Statistica, version 13 (Copyright 1984–2018 TIBCO Software Inc. All rights reserved, License No. JPZ804I382130ARCN10-J). The significance of differences between the compared values was determined by Student's t-test. Normality of quantitative characteristics distribution was analyzed using the Shapiro–Wilk test [3]. Descriptive statistics of non-normally distributed parameters were presented as medians and interquartile ranges, Me (Q25; Q75) [8]. The significance of differences between the compared values was determined by the Mann–Whitney test [1,2]. All the tests were two-tailed. The difference was considered statistically significant at a level of P (P-value) <0.05.

Results

We have found that the use of the immunomodulator azoximer bromide in combined therapy in children with new TB cases after AMBT MF helped to normalize all indicators of the cytokine profile and the balance in the regulatory system of anti-inflammatory cytokines [4].

The frequency of culture positivity was not significantly different between children of both groups at the beginning of AMBT. Namely, positive cultures were diagnosed in 11 (42.3 %) children of the main group and 11 (44.0 %) – of the control group. In the course of treatment, the average time of culture conversion was significantly shortened by 0.9 (1.5 (1.0; 2.0) months in children of the main group against 2.4 (2.0; 3.0) months in the control group ($P < 0.01$). And that was despite the fact that multidrug-resistant strains of *Mycobacterium tuberculosis* (MBT) were detected in both groups with almost equal frequency during the treatment, and the diagnosis of a new case of drug-resistant tuberculosis (DR-TB) was re-registered into multidrug-resistant TB (MDR-TB)/(Rif-TB): 4 (15.4 %) children in the main group and 4 (16.0 %) children in the control group.

There was not a significant difference in the frequency of clinical forms between both groups of children with new TB cases (*Fig. 1*): infiltrative form was diagnosed in 9 (34.6 %) children of the main group and in 11 (44.0 %) – of the control group, disseminated form – in 6 (23.1 %) and 7 (28.0 %), respectively, primary tuberculosis complex (PTC) – in 6 (23.1 %) and 7 (28.0 %), respectively. In addition, in 5 (19.2 %) children of the main group, infiltrative tuberculosis of intrathoracic lymph nodes (TITLN) was determined.

Radiologically, at the end of AMBT MF (*Fig. 2*), the frequency of positive dynamics was 1.8 times significantly higher in the main group compared with the control one: 20 (77 %) children against 11 (44 %) ($\chi^2 = 5.79$; $P < 0.01$). Stable radiological dynamics was diagnosed in only 3 (11.5 %) children of the main group. The lack of radiological dynamics was in 3 (11.5 %) children of the main group and in 8 (32 %) – of the control group. Negative and weakly positive radiological dynamics was seen only in the control group: in 3 (12 %) and 3 (12 %), respectively.

The frequency of destructive process at the beginning of treatment in both groups did not differ significantly and

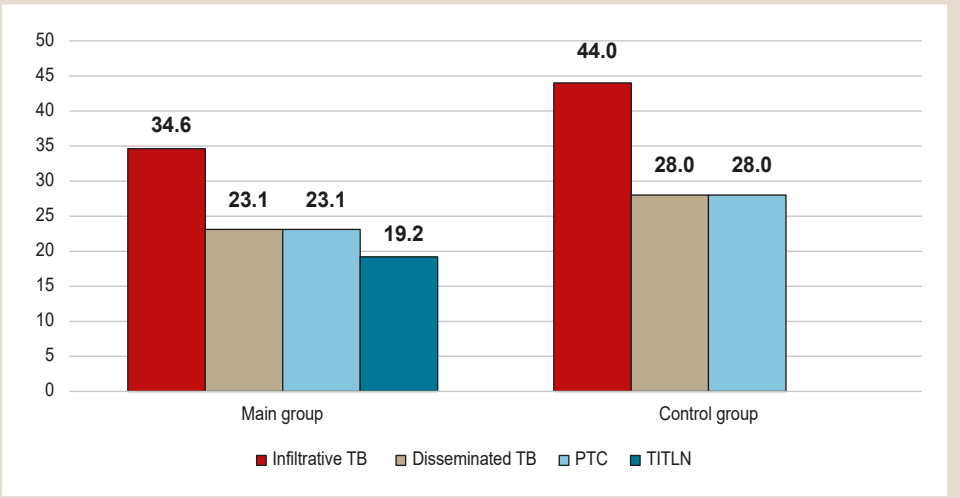

Fig. 1. The frequency of clinical forms in children with new TB cases, %.

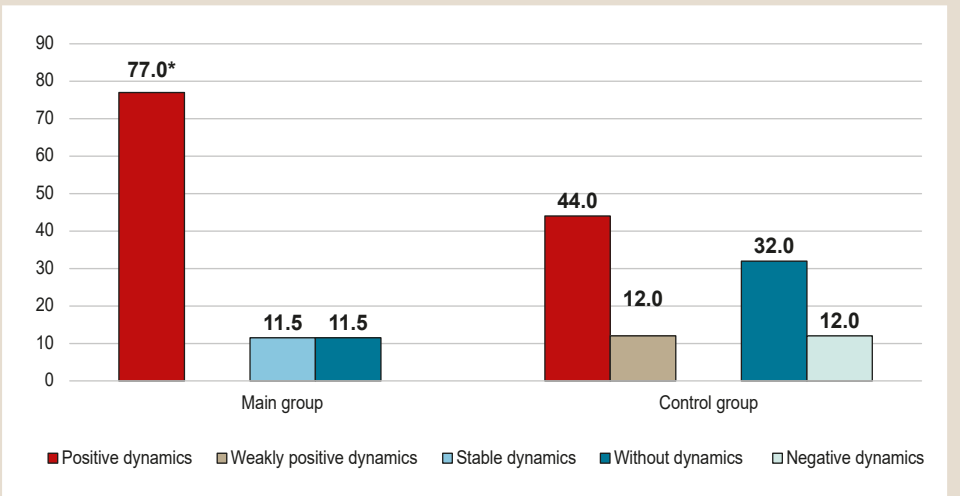

Fig. 2. Radiological dynamics in children with new TB cases on the background of immunocorrection in combined treatment at the end of AMBT MF, %.

*: significant difference between the groups ($P < 0.05$).

was registered in 6 children (23.1 %) of the main group and 5 (20.0 %) children – of the control group. However, in the main group, the destruction healing was significantly 2.1 months shorter than in the control group: 1.7 (1.0; 2.0) months against 3.8 (3.0; 4.0) months ($P < 0.02$).

The tolerability of combined treatment with immunomodulator azoximer bromide in all 26 (100 %) children was satisfactory. Children, who received only AMBT, reported isolated cases of side effects, such as nausea and weakness, which did not require AMBT withdrawal being eliminated within 2 weeks.

Fibrobronchoscopy (FBS) revealed changes in the tracheobronchial tree in 13 (50 %) children of the main group and in 8 (32 %) – of the control group. Bronchial tuberculosis was diagnosed in 11 (42.3 %) children (among 7 (26.9 %) of them, infiltrative form was diagnosed, infiltrative-fistulous – in 2 (7.7 %) and fistulous – in 2 (7.7 %)), and 2 (7.7 %) children had diffuse endobronchitis. In the control group, bronchial tuberculosis was detected in 6 (24 %) children, of whom 5 (20 %) – infiltrative and 1 (4 %) – infiltrative-fistulous. Diffuse endobronchitis in the control group was diagnosed in 2 children (8 %). In the course of treatment, fibrobronchoscopic changes healed in both groups.

At the beginning of treatment, the general condition was considered as satisfactory in 20 (76.9 %) children of the main group and in 23 (92.0 %) – of the control; as moderate – in 5 (19.2 %) and 2 (8.0 %), respectively, as severe – only in 1 (3.9 %) child of the main group. 13 children (50.0 %) of the main group and 7 (28.0 %) of the control one had complaints. 10 children (38.5 %) of the main group and 3 (12.0 %) of the control group complained of cough, 6 (23.1 %) and 3 (12.0 %) – of weakness, respectively. Intoxication syndrome was diagnosed in 6 children (23.1 %) of the main group and in 2 (8.0 %) – of the control one. In the treatment course, the time of clinical symptom disappearance did not differ significantly between the groups and averaged 1.5 months.

The average time of the AMBT main course was significantly 1.5 months shorter in the main group children: 6.2 (5.6; 6.8) months against 7.7 (6.0; 9.3) months in the control group ($P < 0.01$). And that was despite the fact that new DR-TB cases, which were included in the study, were re-registered into category 4 in the process of treatment: 7 (26.9 %) cases in the main group and 8 (32.0 %) cases in the control group.

Discussion

Given the results obtained, the use of immunomodulator azoximer bromide in the complex treatment for children

with new TB cases, alongside normalization of all cytokine profile indicators and the balance in the regulatory system of pro- and anti-inflammatory cytokines [4], helped to achieve by the end of treatment: a shorter average time to culture conversion by 0.9 (1.5 (1.0; 2.0) months against 2.4 (2.0; 3.0) months; P < 0.01), positive radiological dynamics of 77 % (χ^2 = 5.79; P < 0.01), reduced time of destruction healing by 2.1 (1.7 (1.0; 2.0) months against 3.8 (3.0; 4.0) months, P < 0.02), shorter average time of the basic AMBT course by 1.5 (6.2 (5.6; 6.8) months against 7.7 (6.0; 9.3) months; P < 0.01). Combined treatment tolerability was satisfactory in all 100 % of cases. Combined treatment tolerability was satisfactory in all 100 % of cases.

Since we have not found researches in the available literature focused on the effect of immunomodulator azoximer bromide on the effectiveness of combined therapy in TB children, we could not compare the data obtained with findings reported by other scientists, that makes this work unique.

The data obtained on the high effectiveness of immunomodulator azoximer bromide in the combined treatment of TB patients, however, have confirmed the literature data on the need to use immunomodulators for this category of patients [11,15].

Conclusions

Immunomodulator azoximer bromide as a part of the combined therapy for children with new TB cases can not only restore the body immune reactivity, but also reduce the specific process activity on the background of AMBT, shorten the average time to culture conversion by 0.9 months and destruction healing by 2.1 months, reduce the average duration of the main AMBT course by 1.5 months. In addition, this approach to therapy helps to conduct standard AMBT without changing the treatment regimen.

Prospects for further research. To study immunological changes in children with new MDR-TB cases.

Conflicts of interest: authors have no conflict of interest to declare.
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