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Evaluation of the effectiveness of bedaquiline and delamanid treatment among children and adolescents with multi-drug-resistant pulmonary tuberculosis

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Introduction. Against the backdrop of multiple and widespread drug resistance of Mycobacterium tuberculosis (MDR-TB), there has been a significant decline in the effectiveness of treatment of tuberculosis (TB) patients in Ukraine and globally. Therefore, in recent years, new antimycobacterial drugs, such as bedaquiline (Bdq), delamanid (Dlm) and pretomanid, have been introduced to improve treatment efficacy in adults, children and adolescents.

Purpose. To study the effectiveness of complex treatment with bedaquiline (Bdq) and delamanid (Dlm) in children under 18 years old with multiple and extensively drug-resistant pulmonary TB (MDR/XDR-TB).

Materials and methods. To study the clinical efficacy of chemotherapy with Bdq and Dlm, a retrospective cohort analysis of medical records was conducted. The main group consisted of 40 children with MDR/XDR-TB who received comprehensive antimycobacterial therapy with Bdq and Dlm; and the control group consisted of 27 patients who received treatment without Bdq and Dlm.

Results. It was found that during the first three months of treatment, there was a decrease in bacilli in all patients treated with Bdq and Dlm and in the group of patients without these new drugs (control), but in the control group, the decrease was significantly slower, $p<0.05$. According to the immune system parameters, after the intensive phase was completed, the activity of a specific process was 1.7 times more frequent in patients of the control group than in the main group.

After completion of the course of treatment, all patients in the main group showed resorption of infiltration, compaction of foci, and formation of fibrosis in the lungs according to the results of X-ray tomographic examination. However, in 14.8% of patients in the control group, treatment failure was noted with the resumption of bacterial release and destruction in the lung tissue, and in the main group, all patients had healing of the decay cavities. In the majority (77.5%) of patients in the main group, treatment resulted in the formation of small residual changes, but large residual changes were 2.3 times more common in the control group in the form of multiple dense foci, fibrosis and residual decay cavities.

Conclusions. Studies have shown the high efficacy of complex treatment with Bdq and Dlm in children and adolescents. In particular, in MDR/XDR-TB patients treated with Bdq and Dlm, treatment results were 2 times more likely to be considered «cured» than in the control group, and 1.5 times less likely to be considered «complete». The treatment success rate in the main group was 100.0%, and in the control group — 85.2%.

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

No conflict of interests was declared by the authors.

Keywords: children, tuberculosis, adolescents, multidrug resistance, extensive drug resistance, treatment, bedaquiline, delamanid.

Оцінка ефективності лікування бедаквіліном і деламанідом дітей та підлітків, хворих на множинний лікарсько-стійкий туберкульоз легень

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Вступ. На тлі множинної і широкої лікарської стійкості мікобактерій туберкульозу (МБТ) спостерігається суттєве зниження результативності лікування хворих на туберкульоз (ТБ) в Україні і у світі. Тому останніми роками для підвищення ефективності лікування впроваджуються нові антимікобактеріальні препарати, такі як бедаквілін (Bdq), деламанід (Dlm) і претоманід, як у дорослих, так і в дітей та підлітків.

Мета — вивчити ефективність комплексного лікування із застосуванням бедаквіліну (Bdq) і деламаніду (Dlm) у дітей віком до 18 років, хворих на множинний і широкий лікарсько-стійкий ТБ легень (МЛС/ШЛС-ТБ).

Матеріали та методи. З метою вивчення клінічної ефективності хіміотерапії з Bdq і Dlm проведено ретроспективний когортний аналіз даних медичної документації. Основну групу становили 40 дітей, які хворіли на МЛС/ШЛС-ТБ і отримували комплексну антимікобактеріальну терапію з Bdq і Dlm; а контрольну — 27 хворих, які отримували лікування без Bdq і Dlm.

Результати. Встановлено, що протягом перших трьох місяців лікування відмічалося знебацилення в усіх хворих, що отримували Bdq і Dlm, і в групі хворих без цих нових препаратів (контрольна), проте в контрольній групі знебацилення відбувалося вірогідно повільніше, $p<0,05$. За даними показників імунної системи, після завершення інтенсивної фази в 1,7 раза частіше у хворих контрольної групи, ніж в основній, зберігалась активність специфічного процесу.

Після завершення курсу лікування в усіх хворих основної групи за результатами рентгено-томографічного обстеження спостерігалося розсмоктування інфільтрації, ущільнення вогнищ, формування фіброзу в легенях. Проте в 14,8% пацієнтів контрольної групи відмічалася неуспішність лікування з відновленням бактеріовиділення і деструкції в легеневій тканині, а в основній — відбулося загоєння порожнин розпаду в усіх обстежених. У більшості (77,5%) пацієнтів основної групи лікування завершилося формуванням малих залишкових змін, проте великі залишкові зміни в 2,3 раза частіше спостерігалися в контрольній групі у вигляді множинних щільних вогнищ, фіброзу і залишкових порожнин розпаду.

Висновки. Дослідження засвідчили високу ефективність комплексного лікування із застосуванням Bdq і Dlm у дітей і підлітків. Зокрема, у хворих на МЛС/ШЛС-ТБ, які отримували комплексну терапію з Bdq і Dlm, результати лікування у 2 рази частіше розцінювалися як «виліковано», ніж у контрольній групі, і в 1,5 раза рідше — як «завершено». Успішність лікування в основній групі становила 100,0%, а в контрольній — 85,2%.

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: діти, туберкульоз, множинна лікарська стійкість, широка лікарська стійкість, лікування, бедаквілін, деламанід.

Tuberculosis (TB) remains one of the most urgent problems of health care and one of the leading causes of death in the world. TB is a disease which has no borders and no social and age restrictions. Recently, in Ukraine there has been an increased rate of the latent tuberculous infection (LTBI) of the population, which increases according to the age. LTBI among children aged 7–8 years is 8.5%, at the age of 13–14 years — up to 20–25%, and this indicator significantly increases in the contact children and adolescents from focies of tuberculous infection [24].

Ukraine is one out of ten countries with the highest burden of multidrug-resistant pulmonary and extrapulmonary tuberculosis (MDR-TB) [15,16,19]. On the background of positive dynamics of the reduction of mortality and incidence of new cases of TB the situation with MDR-TB has been ambiguous in recent years. In Ukraine scientific works carried out by V.M. Melnyk et al. [16] proved that a negative trend is an increase of frequency of MDR-TB from 27.3% in 2016 to 29.0% in 2018, the increase in the number of confirmed cases of extensive drug-resistant TB (XDR-TB) up 8.9%.

In recent years in Ukraine and in the world it is observed the increase in the incidence of resistant forms of pulmonary TB among the adult population. The proportion of MDR, XDR and resistance to rifampicin (Rif-TB) of *Mycobacterium tuberculosis* (MBT) among children under 18 years old with firstly detected tuberculosis (FDTB) has significantly increased too [2,4–6,11,12,14].

There is a significant decrease in the effectiveness of the treatment among the patients in Ukraine and in the world on the background of MDR-TB and XDR-TB [10,15]. The insufficient effectiveness of chemotherapy regimens (CTRs), which were based on traditional antimycobacterial drugs (AMDs) second-line, and the accumulation of the evidence base regarding new AMDs became a factor in improving existing treatment and forming regimens with the use of new AMDs, such as bedaquiline (Bdq), delamanid (Dlm) and pretomanid (Pa) both among adults, children and adolescents [1,3,7,10,14,15,17,18,20–24].

In the medical literature, a little number of studies is devoted to the issue of the effectiveness of the treatment of Bdq and Dlm among children and adolescents [8,9,13]. In this regard, it is important to determine the effectiveness and tolerability of new AMDs in children and adolescents with MDR/XDR-TB.

The purpose of the work — to study the effectiveness of complex treatment with Bdq and Dlm in children under 18 years old with multiple and extensively drug-resistant pulmonary TB (MDR/XDR-TB).

Materials and methods of the research

A retrospective cohort analysis of medical files in order to study the clinical effectiveness of chemotherapy (CT) with Bdq and Dlm was conducted. The main group was formed of 40 patients who had MDR/XDR-TB and received complex antimycobacterial therapy (AMBT) with Bdq and Dlm. Children from 0 to 14 years old constituted 25 (62.5%), and 15 (37.5%) were teenagers from 15 to 17 years old. There were 18 (47.5%) boys, 22 (52.5%) girls. The control group consisted of 27 patients who received complex AMBT without Bdq and Dlm: there were 17 (62.9%) children and 10 (37.1%) teenagers.

Patients of the main group received [bedaquiline (Bdq) + delamanid (Dlm) + linezolid (Lzd) + clofazimine (Cfz) + cycloserine (Cs)] for 6 months and + 12–14 months of [Bdq+Dlm+Lzd+Cfz]. Depending on the drug sensitivity test (DST) of a patient or the source of the TB infection, the main group was given other AMBPs if necessary. If one or two drugs were used from group A in AMBT, then two AMBDs from group B were added. If it was impossible to make an effective AMB regime from four AMBDs of groups A and B, then AMBDs from group C were prescribed: ethambutol (E), Dlm, pyrazinamide (Z), imipenem/cilastine, meropenem, amikacin, ethionamide, para-aminosalicylic acid. The individualized treatment regimen was long-term — up to 18–20 months. The total duration of CT was reduced to 15–17 months after cultural conversion of sputum.

The control group received CTR without Bdq and Dlm. They were given [pyrazinamide (Z) + kanamycin (Km) or (capriomycin (Cm) + levofloxacin (Lef) or moxifloxacin (Mfx) + prothionamide (Pt) + cycloserine (Cs)] for 8 months and + 12 months of [Z Lef/Mfx Pt Cs]. The dose of AMBDs was calculated according to the patient's body weight. In accordance with the calendar monitoring of treatment of TB patients, the monitoring of treatment effectiveness was carried out [11].

The evaluation of the effectiveness of AMBT was carried out according to the following objective criteria: disappearance of clinical symptoms, frequency and time of the cessation of bacterial

Table 1

Distribution of tuberculosis patients according to clinical forms, the presence of destruction in the lungs and treatment regimes, abs. (%)

Clinical form of tuberculosis	Control group (n=27)		Main group (n=40)	
	All	Destruction	All	Destruction
Infiltrative tuberculosis	9 (33.4)	6 (66.7)	15 (37.5)	10 (66.7)
Disseminated tuberculosis	8 (29.6)	6 (75.0)	13 (32.5)	10 (76.9)
Primary tuberculous complex	5 (18.5)	3 (60.0)	9 (22.5)	5 (55.5)
Tuberculosis intrathoracic lymphatic nodes	5 (18.5)	1 (20.0)	3 (7.5)	1 (33.3)
All	27 (100.0)	16 (59.3)	40 (100.0)	26 (65.0)

Table 2

The frequency and time of cessation of bacterial excretion, resolution of focal and infiltrative changes in the examined groups, depending on treatment regimens

Parametr	Time (month)	Groups			
		Control (n=27)		Main (n=40)	
		abs.	%	abs.	%
Bacterial excretors	–	19	70.3	26	65.0
Frequency of cessation of bacterial excretion	1	7	36.8	16	61.5*
	2	10	52.6	9	34.6
	3	2	10.6	1	3.9*
Positive X-ray dynamics (by frequency of partial resorption of focal and infiltrative changes)	3	5	18.5	15	37.5*
	6	7	25.9	17	42.5
	9	10	37.1	4	10.0*

Note: * — the difference is significant in relation to the control group ($p<0.05$).

excretion according to the data of microscopy and culture on nutrient media, the time of closure of decay cavities.

Children and adolescents with MDR-TB were treated in the pediatric departments of the CU ENT «Pulmonology Lviv Regional Diagnostic Center», the Volyn Regional Phthisiopulmonology Medical Center, the Khmelnytskyi Regional Phthisiopulmonology Medical Center and the Chernivtsi Regional Clinical Anti-Tuberculosis Dispensary.

Results and discussion of the research

The researched groups were identical in the distribution of clinical forms, the presence of destructive changes in the lung tissue and the structure of the resistance of pathogen to AMBDs. The distribution of TB patients is shown in Table 1. Infiltrative TB was diagnosed among 9 (33.4%) patients of the control group and among 15 (37.5%) patients of the main one, disseminated — among 8 (29.6%) patients and 13 (32.5%) patients respectively, primary tuberculous complex (PTC) — among 5 (18.5%) patients and 9 (22.5%) patients respectively, and TB intrathoracic lymphatic nodes (TB ITLN) — among 5 (18.5%) patients and 3 (7.5%) patients respectively.

The presence of decay cavities in the lungs was ascertained in 26 (65.0%) patients of the main group and in 16 (59.3%) of patients of the control one. At the same time, in 52.0% (13 out of 25) children and in 86.7% (13 out of 15) teenagers the presence of decay cavities was ascertained, that is, the destruction was 1.7 times more often ascertained in teenagers in comparison with children.

The research showed the following changes in the clinical course of TB within 3 months of anti-TB treatment as the reduction of symptoms of intoxication, the cessation of cough in 87.5% (22) of children and 70.3% (10) of adolescents, the cessation of catarrhal phenomena in the lungs, the positive dynamics in blood parameters.

The data on the frequency and time of cessation of bacterial excretion are presented in Table 2.

In 70.3% (19 out of 27) patients of the control group and in 65.0% (26 out of 40) of patients of the main one, bacterial excretion was established. Other patients were diagnosed with the risk of MDR-TB, because they did not have a respiratory sample to determine MBT.

One of the important criteria for evaluating the effectiveness of anti-TB treatment is the rate of the end of bacterial excretion. It was established that within the first three months of AMBT in both groups in 100% of cases the end of bacterial excretion was achieved. However, among patients who received AMBT with Bdq and Dlm, the end of bacterial excretion occurred faster. Within the first month of treatment the highest indicator of the halt of bacterial excretion was found

Table 3

The frequency and time of closure of decay cavities (healing of destruction) in the researched groups depending on the treatment regimens

Group		All	The time of closure of decay cavities (months)			Availability of decay cavity
			3	6	9	
Control	abs. (%)	16 (59.2 %)	2 (12.4)	4 (25.0)	5 (31.3)	5 (31.3)
Main	abs. (%)	26 (65.0 %)	6 (23.1)*	13 (50.0)*	4 (15.4)*	3 (11.5)*

Note: * — the difference is significant in relation to the control group ($p<0.05$).

in patients of the main group — 61.5% (16) of patients in comparison with the control one 36.8% (7) of patients, $p<0.05$. In two months, bacterial excretion stopped in 96.2% (25) of patients and 89.5% (17) of patients, respectively. After three months of CT — in 100% (40) of patients.

In researched patients regarding the resorption of foci and infiltration, a similar regularity was established. In particular, within 9 months among 81.5% (22 out of 27) of patients of the control group and in 90.0% (36 out of 40) of patients of the main one, significant positive X-ray dynamics were established. Therefore, foci and infiltration radiographically were detected in 5 (18.5%) patients who did not receive Bdq and Dlm and in 4 (10.0%) patients — who received new AMBDs ($p<0.05$) after 9 months of treatment.

Among all patients of the main group at the end of the course of anti-TB treatment the resolution of infiltration, the densification of foci, the formation of fibrosis in the lungs was confirmed radiologically. However, in 4 (14.8%) patients of the control group, the failure of treatment with the restoration of bacterial excretion was confirmed.

The destruction in the lungs at the X-ray-tomographic examination was found in 52.0% (13) of children and 86.7% (13) of adolescents. The majority of patients of the main group (73.1% total for 6 months), who received Bdq and Dlm within 6 months of treatment healed of decay cavities, and at 9 months the healing was noted in other 4 (15.4%) patients (Table 3). After 9 months the destruction was observed among 2 (7.7%) patients of the main group.

At the same time, the healing process of decay cavities (destruction) in the control group probably occurred more slowly. In particular, among the control group the healing of the destruction within 6 months was found almost 2 times less often in comparison with the main one (37.4% vs. 73.1%; $p<0.05$). In the dynamics within 9 months among the control group, the destruction healed in 31.3% patients, but after 9 months of the treatment without Bdq and Dlm in 5 (31.3%) cases a decay cavity was detected. Thus, among patients who received new AMBDs, after 9 months of treatment a destruction was found in only 3 (11.5%) patients and in the control group — in 5 (31.3%). However, at the end of anti-TB treatment among 12.5% (2 out of 16) of patients of the control group a destruction was observed, and among the main one the decay cavities healed in all the researched patients.

Our research shows that on the background of AMBT in patients with TB, certain changes in the immune system occur due to a decrease of the antigenic load on the defense system with an optimally selected treatment regimen. We have chosen the most informative tests: CD3+, CD4+, CD8+, CD4+/CD8+, pro-inflammatory interleukins (IL 6 and IL 10) to evaluate the effectiveness of the complex treatment for patients with drug-resistant TB (DR-TB) (Table 4).

In particular, at the end of the intensive phase in 3 (25.0%) patients of the control group and in 4 (36.4%) of the main one, a normalization of the total number of CD3+ T-lymphocytes occurred. A state of dynamic equilibrium between subpopulations T-helper and T-suppressor lymphocytes, CD4+/CD8+ in the main group (6 (54.5%) persons) 1.6 times was more often restored in comparison with the control one and in 4 (33.3%) persons of the control group. The level of circulating immune complexes (CIC) was normalized in 4 (33.3%) patients of the control group and in 6 (54.5%) of the main one at the end of the intensive phase. Therefore, at the stage of completion of the intensive phase of AMBT with the use of Bdq and Dlm, the normalization of cellular and humoral immunity indicators occurred 1.5 times more often (43.4±4.5)% vs. (29.6±2.8)% ($p<0.05$), which indicates on the effectiveness of complex therapy. However, according to the indicators of the immune system in the control group the activity of the specific process remained more often (70.4% vs. 56.6%; $p<0.05$) at the end of the intensive phase rather than in the main one.

Table 4

The frequency of normalization of indicators of cellular and humoral immunity at the stage of completion of the intensive phase of treatment among patients with drug-resistant pulmonary tuberculosis, depending on treatment options

Indicators	Groups			
	Control (n=12 patients)		Main (n=11 patients)	
	abs.	%	abs.	%
CD3+	3	25.0	4	36.4
CD3+CD4+	4	33.3	4	36.4
CD3+CD8+	3	25.0	4	36.4
CD3+CD4+/CD3+CD8+	4	33.3	6	54.5*
TNF-α/IL 10	3	25.0	4	36.4
IL 6/IL 10	3	25.0	4	36.4
IgA	4	33.3	5	45.5
IgM	4	33.3	6	54.5*
Circulating immune complexes	4	33.3	6	54.5*
On the average (%)	(29.6±2.8)		(43.4±4.5)*	

Note: * — the difference is significantly relative to the control group (p<0.05).

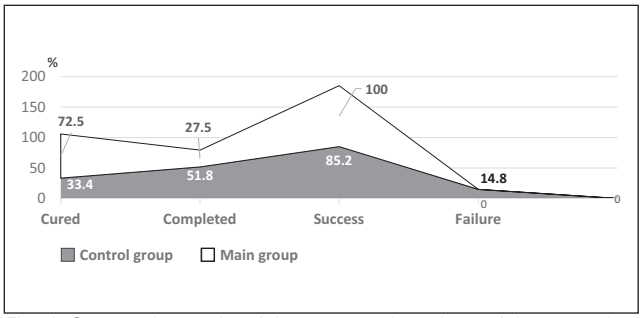

Fig. 1. Comparative results of the treatment in patients of the researched groups based on the cohort analysis (%)

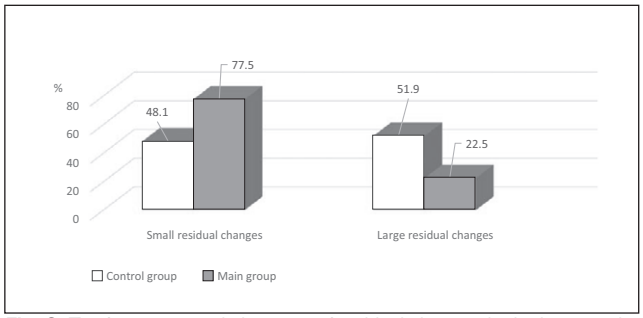

Fig. 2. The frequency and character of residual changes in the lungs at the end of anti-TB treatment in patients depending on the treatment options

Cohort analysis showed that in 29 (72.5%) patients of the main group, the result of treatment was considered as «cured» and in 11 (27.5%) patients as «completed» (p<0.05). At the same time, the result of the treatment in the control group was more likely to be stated as «completed» than «cured» (51.8% vs. 33.4%; p<0.05) (Figure 1). In the control group «treatment is completed» is stated more often than in the main one (51.8% vs. 27.5%; p<0.05) and 2 times less often — «cured» (33.4% vs. 72.5%). According to our research, the success rate of the treatment in the main group was 100.0% and in the control one — 85.2%. Therefore, the treatment failure in the control group was 14.8%.

The anti-TB treatment ended with the formation of small residual changes among most patients of the main group (77.5%). However, large residual changes as multiple dense foci, fibrosis and residual decay cavities in the control group were observed 2.3 times more often (51.9% vs. 22.5%; p<0.05) compared to the main one (Figure 2).

Conclusions

Our research shows that for all patients who received Bdq and Dlm and the group without these new AMBDs, the end of bacterial excretion was established within the first three months of treatment. However, in the control group the halt of bacterial excretion probably occurred more slowly.

In 5 (18.5%) patients who did not receive Bdq and Dlm and in 4 (10.0%) persons who had new AMBDs (p<0.05), foci and infiltration were found radiologically after 9 months of AMBT. During the same period of CT among the patients receiving Bdq and Dlm, the destruction was found in only 2 (11.5%) patients and in the control group — in 5 (31.3%).

The normalization of immunological parameters in (29.6±2.8)% of the control group and in (43.4±4.5)% of the main one (p<0.05) was noted at the end of the intensive phase of AMBT. A significant difference between the

researched groups was obtained from the immunoregulatory index CD3+CD4+/CD3+CD8+, IgM and CIC. Positive dynamics of immunological changes were 1.5 times more often detected in children and adolescents who received Bdq and Dlm. It indicated a decrease in antigenic load, the phenomena of TB intoxication and increased effectiveness of AMBT.

The resolution of infiltration, the densification of the foci and the formation of fibrosis in the lungs in all patients of the main group were ascertained during the X-ray-tomographic examination at the end of the treatment. However, in 4 (14.8%) patients of the control group, the treatment failure with the restoration of bacterial excretion was diagnosed and they were diagnosed with the destruction in the lung tissue. In the main group, the decay cavities healed in all patients.

In the main group compared to the control one, it was 2 times more often stated as «cured» (72.5% vs. 27.5%; $p<0.05$) and 1.5 times less often as «treatment completed» (33.4% vs. 72.5%). The success rate of the treatment in the main group was 100.0% and in the control one — 85.2%. It indicates the high effectiveness of complex AMBT using Bdq and Dlm among children under 18 years old.

No conflict of interests was declared by the authors.

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