IJISET - International Journal of Innovative Science, Engineering & Technology, Vol. 6 Issue 10,October 2019
ISSN (Online) 2348 – 7968 | Impact Factor (2019) – 6.248
www.ijiset.com

Efficacy of Tuberculosis Treatment in Patients with Malabsorption Syndrome During IV Administration of Drugs

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Background:

Purpose: Assessment of treatment efficacy of sensitive tuberculosis with severe intestinal absorption impairments during IV administration of anti-tuberculosis drugs.

Materials and methods: Open-label, randomized, parallel-group, reference-controlled clinical study in 56 patients with sensitive firstly diagnosed lung tuberculosis (SFDT).

Results: Decreased absorption in small intestine is observed in 58.9% of cases of firstly diagnosed tuberculosis with maintained sensitivity and predominant decreasing intestine penetration indicator 3.1 to 6 (in 21.9% of cases) and accompanied, according to pathomorphological data, by both impaired para- and transcellular transport of nutrients by epithelial cells of small intestine and decreasing area of intestinal absorption. The severest negative impact on treatment efficacy in patients with firstly diagnosed tuberculosis is a severe grade of impaired absorption in small intestine (IPI less than 3) – malabsorption syndrome.

Conclusion: In patients with sensitive firstly diagnosed lung tuberculosis with moderate and severely impaired absorption in small intestine, optimized schemes of etiotropic treatment in intensive phase using IV forms allowed to reliably reduce duration period of intoxication syndrome in 1.5 times, bronchopulmonary dysplasia – in 1.4 times; accelerated normalization of hemogramme indicators and endogenous intoxication indices; increased frequency of bacterioexcretion discontinuation in 2.1 times and frequency of positive X-Ray dynamics in 1.5 times.

Key words: tuberculosis, malabsorption syndrome, treatment of tuberculosis.

INTRODUCTION

The latest data of TB treatment results published by WHO showed that efficient treatment indicator was 83% (cohort of 2014) in specific WHO indicator no less than 90%. [1,2] Globally, unhealed TB has a serious public health hazard in general, as disease is spread through the air, i.e. one person with TB can infect ten or more people, if he/she is not effectively treated and takes no safety measures of infection control. Thus, global progress in implementing strategy "End TB" depends on effective problems solving with regard to increasing efficacy of TB treatment, as this allows to break epidemiological chain in the most effective way.

Foreign and domestic investigators constantly search for reasons and ways to increase efficacy of anti-tuberculosis therapy. [3,4,5,6] However, TB causative agent nature, medical and social factors obstruct the aim achievement [7,8]. According to WHO data, in Ukraine increase rate of TB treatment efficacy is the lowest among the EU countries, especially among people living with HIV/TB co-morbidity and drug-resistant tuberculosis (DRTB) . [7,9,10,11]

To date, it is established that decreased efficacy of TB treatment and development of mycobacterium tuberculosis resistance are greatly related to reduction of anti-mycobacterial drugs concentration (AMBD) in blood below therapeutic level. [8,2] The most frequent reasons of this is insufficient dosage of anti-tuberculosis drugs (ATD) and irregular administration due to low adherence of patients to treatment. [2,5] However, as multiple studies show, efficacy of TB treatment depends not only on efficacy of etiotropic therapy but also on state of functional organsresponsible for normal pharmacokinetics and pharmacodynamics of medicinal products as well as presence of concomitant diseases and pathological states that are aggravating immune system dysregulation and supporting maintenance and increase of specific inflammatory reactions. [1,13,14] In particular, special attention in this aspect should be paid to digestive system pathology which in its frequency ranks as second in structure of concomitant diseases with TB. [8,11]Important role in efficient TB treatment depends on normal functional state of small intestine in which absorption of AMBD takes place. [15,16] In a proportion of patients due to long-term endogenous intoxication, low nutritive status, ATD toxic effect on small intestine mucosa, malabsorption syndrome develops which can be considered not only as a reason of low-efficacy of treatment but also as a risk factor for drug-resistance to ATD. [17,18]

Characteristics of functionality and morphology of small intestine in patients with lung tuberculosis have been poorly investigated in tuberculous patients and these characteristics can play a key role in increasing treatment efficacy indicator due to methodology of improving treatment programme with modification of drug administration to reach the maximum peak concentration and treatment efficacy respectively.

MATERIALS AND METHODS

Efficacy of optimized treatment schemes was investigated in an open-label, randomized, parallel-group, reference-controlled clinical study of efficacy, safety and tolerance of treatment schemes using IV forms of ATD in patients with firstly diagnosed lung tuberculosis with maintained sensitivity to first-line drugs.

The study was conducted taking into account the main provisions of the GCP ICH and the Helsinki Declaration on Biomedical Research (1974), in which the person serves their object and its subsequent revisions (Seoul, 2008), the Council of Europe Convention on Human Rights and Biomedicine (1997) p.) and the recommendations of the Committee on Bioethics at the Presidium of the Academy of Medical Sciences of Ukraine (2002) with the positive conclusion of the bioethics commission of the Bukovinian State Medical University (Protocol No. 4 of December 18, 2014). This involves observing the concept of informed consent of the patient, assessing the risk of harm and benefit, the principle of confidentiality and respect for the patient's personality.

Objects of the study were 56 patients with, according to results of intermediate analysis of the absorption impairment degree in small intestine conducted on the first stage of the study, established impaired absorption in small intestine with intestine penetration indicator (IPI) within 0-3 and (to a smaller extent) IPI 3.1-6. [14,16] Patients were divided into 2 groups (group 1 – main, group 2 – control).

All the patients within the study were examined with lactulose-mannitol test (patent for invention No. 2202794) with determining lactulose and mannitol concentration excreted with urine after oral administration. [19] To determine impaired transcellular transport of enterocytes, mannitol amount in urine was analysed. To determine conditions of molecular transport through close contacts between enterocytes, lactulose amount in urine of the examined patients was analysed in three hours after administration of combination “lactulose + mannitol” [Table 1].

Table 1: Lactulose and mannitol concentration in urine of patients with firstly diagnosed lung tuberculosis with maintained sensitivity (M±m)

Indicator	PHP n=30	Group 1 n=28	Group 2 n=28
	median (interquartile range)		
Lactulose concentration in urine (mmol/l)	2.21 (1.7-3.2)	1.98 (1.24-2.42)*	2.17 (1.44-2.78)
Mannitol concentration in urine (mmol/l)	4.99 (4.13-5.91)	4.21 (1.98-5.51)*	3.93 (0.67-4.36)**

Notes: * – indicators are reliably different in the main group and PHP ($p<0.05$); ** – indicators are reliably different in the main groups ($p<0.05$)

Treatment in both the main (group 1 – 28 patients) and the control group (group 2 – 28 patients) in intensive phase of chemotherapy (IPCT) was conducted according to standard scheme (2 HRZE) with appropriate drug dosage for body weight. Optimization of the treatment was performed in group 1 by IV administration of isoniazid (marketing name “bitub”), rifampicin (marketing name “rifonat”), etambutol (marketing name “inbutol”); manufacturer “Yuria-Pharm” and oral administration of pyrazinamide. Patients in the control group (group 2) were treated with tablet forms of ATD. Patients of each examined subgroups were practically of equal age, sex, clinical TB forms. Disseminated clinical TB form, male sex and average age were dominant.

TB treatment efficacy in patients of group 1 and group 2 was assessed according to common criteria: dynamics of clinical TB manifestations; dynamics of bacterioexcretion discontinuation; dynamics of radiological changes.

Analysis of the received data was performed with software packages “STATISTICA 10” (StatSoft Inc., USA) on PC, using parametric and non-parametric methods of calculation. Normality of quantitative data division was determined using Shapiro-Wilk test. To provide statistical data descriptive statistics calculating a mean value, median, minimum and maximum values, standard deviation and 95% CI was used. Probability of possible mistake of each indicator was calculated according to statistical parametric Student’s t-test (normal sample division) and non-parametric Mann-Whitney U test (not normal sample division). Differences between results were considered reliable with $p<0.05$.

Research work is carried out at the expense of the state budget. State registration №0114U002473 “Pathogenetic peculiarities of forming systemic inflammatory response syndrome in extended form of chemoresistance pulmonary tuberculosis improving diagnosis, optimization treatment program and prevention”.

RESULTS AND DISCUSSION. Analysis of the received results of the study showed that reduced small intestine absorption was observed in 58.9% of cases of firstly diagnosed tuberculosis with predominant decreasing IPI 3.1 to 6 (in 21.9% of cases) and accompanied by both impaired para- and transcellular transport of nutrients by epithelial cells of small intestine and decreasing area of intestinal absorption in patients with sensitive first diagnosed lung tuberculosis compared to practically healthy patients (PHP).

To establish reasons of impaired functional small intestine absorption in patients with tuberculosis, prospective pathomorphological study was conducted including 13 cases of deaths

of firstly diagnosed tuberculosis patients with maintained sensitivity. During the study general and special histochemical methods of study were applied, connective tissue state in small intestine structures was assessed, organization of nuclear chromatin and a degree of protein modification were assessed, limited proteolysis in epithelial cells was assessed, micromorphometric methods of study were applied. [19,20]

Assessing results of the study, presence of atrophic and sclerotic changes in small intestine wall were detected. Atrophic changes were mucosal thinning, changes in intestinal villi forms and sizes, reduction in their density compared to control. Crypt depth was not different from normal. Epithelium was high columnar. Epithelial cells were heterogeneous, containing vacuoles in cytoplasm and separated from own plate on different areas.

In some cases, signs of maintained epithelium regeneration namely increasing nuclei and occurrence of mitoses were observed. We detected signs of non-specific mucosal and submucosal inflammation: focal lymphoid cellular infiltrates in mucosal and submucosal layers, moderate plasmocytic infiltration of own plate with a small amount of segmentonuclear leukocytes, separate eosinophils and lymphocytes [Figure 1a, 1b, 1c].

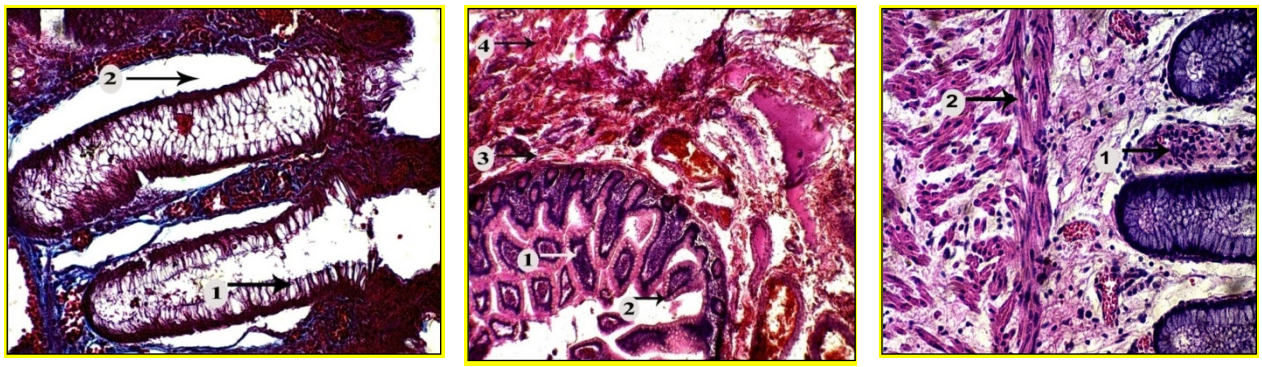


Figure 1:
a. High columnar epithelium with heterogeneous epithelial cells containing vacuoles in cytoplasm (1) and separated from own plate on different areas (2). Hematoxylin and eosin stain. Micrograph. Volume 40x. Circle 10^x.

b. Mucosal thinning, different strand forms and sizes (1). High columnar epithelium with heterogeneous epithelial cells containing vacuoles in cytoplasm (2). Sclerosis of mucosal own plate with focal replacement of own plate (3) and areas of muscular layer by fibrous tissue (4). Hematoxylin and eosin stain. Micrograph. Volume 20^x. Circle 10^x.

c. Signs of non-specific mucosal inflammation: focal lymphoid cellular infiltrates (1), moderate plasmocytic infiltration of own plate with a small amount of lymphocytes (2). Hematoxylin and eosin stain. Micrograph. Volume 40x. Circle 10^x.

It is established that in patients with SFDT micromorphometric tissue indicators were not reliably different from indicators of reference group ($p<0.05$) [Table 2].

Table 2: Morphometric characteristics of small intestine tissue in patients with firstly diagnosed tuberculosis with maintained sensitivity and in reference group (X±Sx)

Indicators	PHP	Firstly diagnosed tuberculosis
Mucosal thickness, μm	767.8±15.19	751.8±12.44*
Strand height, μm	482.9±21.66	475.7±19.07*
Strand width, μm	145.6±8.41	139.1±5.18*
Crypt depth, μm	123.1±2.01	124.2±3.92*
Ratio of strand height and crypt depth	3.92±0.013	3.83±0.024
Specific area of connective tissue, %	11.9±1.12	12.3±1.32
Distance from basal membrane of epithelial cells to capillary wall, μm	8.4±0.41	8.6±0.63

Note: * – CI, $p<0.05$

Thus, in patients with SFDT morphological changes of small intestine wall were detected: pronounced atrophy of mucosal strands, increased specific area of connective tissue and increased distance from basal membrane of epithelial cells to capillary wall which led to decreased absorption surface and impaired absorption that confirms and reliably correlates with the received results of reduced IPI in a proportion of patients with malabsorption syndrome. The received data from themorphological study of small intestine in patients with firstly diagnosed lung tuberculosis is a theoretical background with regard to choosing ways of optimization of anti-tuberculosis therapy and improving pathogenetic treatment.

Based on the received results of the study, a scheme of optimization of etiotropic treatment was developed according to the first category in IPCT with IV administration in the main group of three AMBDs.

Analysing dynamics of clinical TB signs and general patient state, we established that at the moment of discontinuation of IPCT in group 1 general state was satisfactory in 94.1% of patients that is 9.5% more than in group 2 ($p>0.05$). As can be seen from the data in table 3, liquidation frequency of intoxication syndrome (IS) and disappeared/reduced bronchopulmonary syndrome (BPS) in dynamics of treatment in IPCT were not reliably different in group 1 and group 2. However, average terms were significantly reduced in the main group. Thus, average period of disappeared IS in group 1 was 1.5 times less than in the control group ($p<0.05$) as well as for BPS – disappeared symptomatic term was 1.4 times less in group 1 than in group 2, ($p<0.05$).

One of the main efficacy criteria of TB treatment is discontinuation of bacterioexcretion (average terms of smear reversion). In dynamics of optimized treatment, in patients of group 1 with low IPI indicator at the end of IPCT (after 2 months) bacterioexcretion was discontinued in

2.1 times more patients than in group 2 ($p<0.05$) and intensive phase was prolonged to 90 doses in 17.6% of patients of group 1 and in 41.5% of patients of group 2 ($p<0.05$). At the end of the third month of IPCT, in the main group bacterioexcretion was discontinued in the rest 17.6% of patients that is 2.3 times more than in the control group ($p<0.05$). In group 2 after 90 doses of standard scheme of treatment reduced bacterioexcretion intensiveness was observed in one patient (7.7%) and intensive phase was prolonged to 120 doses after which elimination of bacilli was diagnosed in this patient [Table 3].

Table 3: Assessment of clinical sings of firstly diagnosed tuberculosis with maintained sensitivity in dynamics of optimized treatment with reduced small intestine absorption and a low degree of intestine penetration (M±m)

Criteria	Group 1 (main, n=27)	Group 2 (control, n=27)
General state normalization, %	94.1±1.21%	84.6±1.91%
Disappeared from IS till the end of IP, %	94.1±13.91%	84.6±8.82%
Disappeared/significantly reduced sings of BPD till the end of IP, %	88.2±2.14%	76.9±2.35%
Average terms of disappeared IS symptoms, weeks	2.14±0.63*	3.19 ±0.75
Average terms of disappeared BPS symptoms, weeks	4.32±0.69*	5.87±0.71

Note: * – intergroup indicator is reliably different, $p<0.05$

Thus, in dynamics of optimized treatment at the end of IPCT, in group 1 bacterioexcretion was discontinued in 26.1% of cases, in group 2 inefficient treatment was detected. Analysis of terms of bacterioexcretion discontinuation showed that bacterioexcretion was discontinued 0.22 months faster in group 1 than in group 2 [Table 4].

Table 4: Assessment of terms of bacterioexcretion discontinuation in patients with firstly diagnosed tuberculosis with maintained sensitivity with impaired small intestine absorption in dynamics of optimized treatment (M±m)

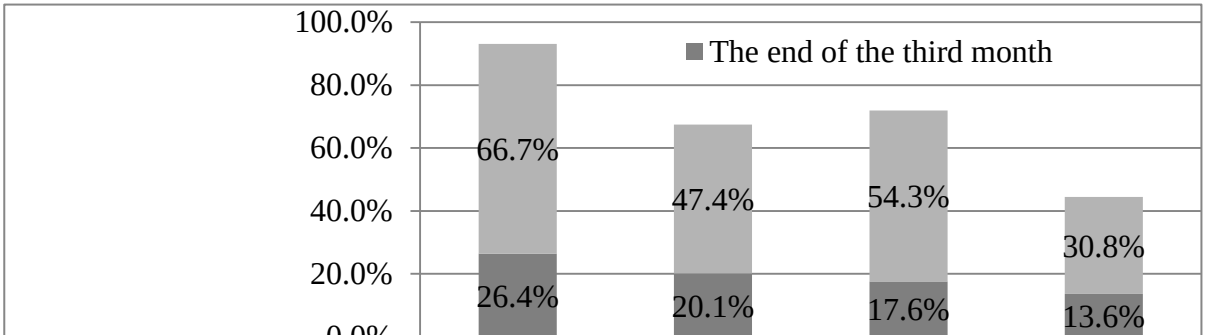
Criteria		Group 1 (main, n=28)	Group 2 (control, n=28)
Terms of bacterioexcretion discontinuation	2 months, %	82.4*	58.5
	3 months, %	17.6*	7.7
	4 months, %	–	7.7
Percent of sputum smear conversion during IP, %		100*	73.9
Average terms of sputum smear conversion, months		2.08±0.39*	2.4±0.79
Bacterioexcretion was not discontinued (inefficient treatment), %		0*	26.1

Notes: * – intergroup indicator is reliably different, $p<0.05$

It should be noted that the severest negative effect on efficacy of treatment is a severe degree of impaired small intestine absorption (IPI less than 3) which is confirmed by results of our study as bacterioexcretion was not discontinued in patients of the control group, malabsorption syndrome was actually diagnosed only in patients with IPI less than 3 that determines this option of impaired small intestine absorption as a direct reason to prescribe IV ATD form. The study results showed that prescription of IV ATD forms in patients with firstly diagnosed lung tuberculosis with concomitant MS allows to obtain the same finished result of treatment as well as in cases of patients with normal and partially reduced IPI.

Dynamics analysis of elimination of bacilli showed pronounced negative effect of malabsorption syndrome on efficacy of TB treatment: in group 1 conversion frequency of sputum smear after the administration of 60 doses of ATD was 1.5 times less than in the control group, after 90 doses of treatment – 1.6 times less ($p<0.05$ in both cases). Treatment frequency without effect in patients with malabsorption syndrome was 2.9 times higher in patients with slightly impaired IPI ($p<0.05$).

One of the qualitative criteria showing TB treatment and prognosis efficacy is radiological dynamics. Figure 2 shows the results of radiological dynamics assessment (reduced sizes and amount of outbreaks, infiltrative changes, cavity decay, increased outbreak intensity) in dynamics of optimized treatment with IV drugs at the end of IPCT in the main and control groups depending on IPI level (subgroup A (IPI-3-6) and B (IPI <3, MS).



	Group 1 A main	Group 2 A main	Group 1 B control	Group 2 B control
The end of the second month	66.7%	47.4%	54.3%	30.8%
The end of the third month	26.4%	20.1%	17.6%	13.6%

Figure 2: Percent of patients with firstly diagnosed lung tuberculosis with maintained pulmonary sensitivity and with different degrees of decreased small intestine functionality with positive radiological dynamics at the end of IPCT

The highest frequency of positive X-Ray dynamics at the end of the second month of treatment was observed in group 1 A – in 66.7% that reliably exceeded the same indicators in group 2 A, group 1 B and group 2 B ($p<0.05$). After 90 doses in group 1 A frequency of positive X-Ray dynamics was 93.1% which is 28% reliably higher than in group 2 A and 23% higher than in group 1 B ($p<0.05$). Low indicators of intestinal absorption had reliable effects on radiological dynamics using only tablet forms in the control groups that accentuate the impact of this parameter on the final indicator of treatment efficacy in patients with tuberculosis. Thus, difference between indicators of group 2A and group 2B is reliable and is 34% ($p<0.05$).

Therefore, established changes of small intestine absorption with reduced small intestine absorptive area have direct impact on ATD absorption and their peak concentrations in blood. Impaired small intestine mucosa functionality is one of the reasons of reduced treatment efficacy and even drug-resistance in specific patients with TB. IV ATD administration allowed to improve treatment efficacy in the main group according to all indicators.

CONCLUSIONS

1. Reduced small intestine absorption was observed in 58.9% of cases of firstly diagnosed tuberculosis with maintained sensitivity with predominant decreasing IPI 3.1 to 6 (in 21.9% of cases) and accompanied, according to pathomorphological data, by both impaired para- and transcellular transport of nutrients by epithelial cells of small intestine and decreasing area of intestinal absorption in patients with sensitive firstly diagnosed lung tuberculosis due to atrophic and sclerotic changes in small intestine wall (mucosal thinning, different strand forms and sizes, reducing their density). Crypt depth was not different from normal. Columnar epithelium was dominant but epithelial cells were heterogeneous, containing vacuoles in cytoplasm and separated from own plate on different areas.

2. The severest negative impact on treatment efficacy in patients with firstly diagnosed tuberculosis is a severe grade of impaired absorption in small intestine (IPI less than 3). Bacterioexcretion was not discontinued in patients of the control group, malabsorption syndrome was actually diagnosed only in patients with IPI less than 3 that determines this option of impaired small intestine absorption as a direct reason to prescribe IV ATD forms.

3. In patients with sensitive firstly diagnosed lung tuberculosis with moderate and severe degree of reduced small intestine absorption, proposed optimized schemes of etiotropic therapy in intensive phase using intravenous forms allowed to reliably reduce duration period of intoxication syndrome in 1.5 times, bronchopulmonary dysplasia – in 1.4 times; accelerate normalization of hemogramme indicators and indices of endogenous intoxication; increase

frequency of bacterioexcretion discontinuation in 2.1 times and frequency of positive X-Ray dynamics by 28% at the end of intensive phase of treatment.

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Pages – 13, picture – 3, number of words – 2460.

Work was performed for state budget funds (state registration number 0114U002473).

"The authors declare no conflict of interest regarding this article".

Concept and design of research - Todoriko L.D., Gumeniuk M.I.
Collection of material - Pidverbetska O.V., Semianiv I.O., Yeremenchuk I.V.
Material handling - Todoriko L.D., Semianiv I.O., Chobotar A.O.
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