ORIGINAL ARTICLE

ANALYSIS OF THE EFFECTIVENESS OF DIFFERENT TREATMENT REGIMENS FOR DRUG-RESISTANT TUBERCULOSIS IN PRYKARPATTIA. CHALLENGES OF OUR TIME

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ABSTRACT

The aim: To study the structure of adverse drug reactions and the effectiveness of treatment among patients with drug-resistant tuberculosis who follow the modified short-term and individualized treatment regimens.

Materials and methods: The analysis of 138 inpatient medical records, outpatient health cards and electronic database of the patient register was conducted. Resistant strains of MTB were microbiologically verified in all the patients. All the patients underwent clinical-laboratory, instrumental microbiological, genetic-molecular (GeneXpert MTB / RIF) methods of examination, both for diagnosis and monitoring of the effectiveness of treatment. In order to prevent complications and control adverse reactions, all the patients were briefly screened for peripheral neuropathy, basic audiometry, the QTc interval was determined, visual acuity and color perception were checked.

Results: At individualized treatment regimen of tuberculosis, adverse reactions were 3.5 times more common than in patients with modified short-term therapy, in 65 (68.4%) cases and in 8 (18.6%) cases, respectively. Accordingly, the effectiveness of treatment differed in both groups. Prevailing in long-term treatment were: treatment interruption treatment gap, treatment failure, continued treatment. In patients receiving short-term regimens, the cured rate was almost twice as common as in the second group.

Conclusions: Timely detection cases of resistant tuberculosis and using linear probe analysis (LPA) - GenoType MTBDRplus for diagnosis of fluoroquinolone resistance, will allow the use of modified short-term treatment regimens for tuberculosis. Which in turn will reduce the number of side effects and improve the outcome of treatment.

KEY WORDS: drug-resistant tuberculosis, genetic-molecular diagnostic, treatment effectiveness, adverse reactions

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INTRODUCTION

Tuberculosis, over many centuries, remains a burning problem facing the medical community. In contrast to the controlled situation of morbidity rates registered in Europe, the persistent TB epidemic in the countries of the so-called "post-Soviet space", to which Ukraine also belongs, draws special attention. An epidemic has been declared since 1995 and has not been overcome yet [1]. Changes in the susceptibility of Mycobacterium tuberculosis (MBT) to antibiotics used in treatment regimens is one of the factors influencing high morbidity rates. The emergence of drug-resistant strains of MTB, due to the discontinued treatment or the so-called defaulted treatment, has led to the development of severe forms of tuberculosis with significant destruction of pulmonary tissue. Prolonged intensive phase, including group-2 injectants, increased incidence of severe adverse reactions, low profiles of safety and evidence of chemotherapy regimens – all of these factors predispose to what we call ineffective treatment. Patient noncompliance in the future will lead to the development of complex types of resistance, when phthisiology depletes the resources of effective drugs – and the next step is palliative care [2].

Having analyzed the findings of the operational studies conducted in Africa, Asia and India, the WHO in 2016 published new guidelines for the management of patients with multidrug-resistant tuberculosis (MDR-TB) [3]. The key differences from the established standards of treatment involved: reduction of the treatment terms to 9-12 months, selection of the individualized scheme for each patient depending on the sensitivity and early recognition of side effects [4]. The production of new highly effective drugs such as linezolid, delamanid, bedaquiline, pretomanid – makes it possible to reduce the number of drugs and significantly reduce the duration of therapy with retention of high effectiveness of treatment before recovery – up to 90% cure rates [5].

Since 2018, the phthisiological reform had started out in Ukraine, which fundamentally changed the treatment approaches in the fight against tuberculosis. Thuswise, it is very important to understand that we should not fight the disease but fight against it. All the possibilities should be engaged in order to prevent the disease, that's why this problem is considered to be a social issue. This is not a duel between a doctor and MTB, but a strategy consisting of a

large number of factors, participants, ways of performing and qualitative resources.

The patient-centered model, which is actively implemented by the Center for Public Health, the Ministry of Healthcare of Ukraine, and scientific-practical phthisiology, requires improvement of the patient's roadmap, starting from the family physician to secondary specialized and tertiary highly specialized care, later on completing treatment under the control of the primary care physician again. Moreover, at all stages the treatment should be identical in its effectiveness and quality in order to achieve a single successful goal – patient's recovery [6].

It is important to realize that victory is impossible without timely diagnosis of tuberculosis, detection of side effects of drugs, and monitoring of the achievements of ultimate goals. We will be able to prescribe effective, short-term treatment regimens only in case of uncompromised patients. That is, those who are diagnosed with resistant tuberculosis for the first time without resistance to fluoroquinolones [7]. So, everything is based on diagnosis. Microbiological detection of MTB and its resistance is of great importance, as it allows to make a correct diagnosis and apply the most effective treatment regimen as soon as possible. Over the past 10 years, the WHO has approved a number of new research methods. Generally, there are four groups of techniques: Xpert MTB/RIF® (Ultra), line probe assay (LPA) – GenoType MTBDRplus, Genoscholar ™ NTM + MDRTB II and GenoType® MTBDRsl [8].

THE AIM

The article analyzes the types and rate of occurrence of adverse reactions to anti-TB agents and the effectiveness of treatment in patients with drug-resistant tuberculosis in Prykarpattia, depending on the chosen treatment regimen. We also set forward the possibilities for timely selection of patients for the administration of modified short-term treatment regimens.

MATERIALS AND METHODS

The study was performed on the basis of communal non-commercial enterprise "Ivano-Frankivsk Regional Phthisiopulmonology Center", Center for Pulmonary Diseases, which provides highly specialized assistance to 1,300,000 people in the region. We have analysed 138 inpatient medical records, outpatient health cards and electronic database of the patient register, which were treated in the department of chemically resistant tuberculosis (XDRTB). Resistant strains of MTB were microbiologically verified in all the patients. According to the strategy in Ukraine, order of the Ministry of Healthcare № 530 from February 25, 2020 "On approval of health standards for tuberculosis", all the patients underwent mandatory examinations, including: laboratory (complete blood count and metabolic panel, urine analysis, the levels of sodium, calcium, potassium, chlorine were detected), creatinine clearance (Cockcroft-Gault formula), instrumental (radiography, computed tomography, spirometry, fibrobronchoscopy, ultrasound of the lungs and abdominal organs), sputum smear microscopy, phenotyping (BACTEC system, Löwenstein-Jensen solid medium (MT molecular-Geneper) / RIF) screening methods, with the aim of proper diagnosing and monitoring of the effectiveness of treatment [8]. The patients also underwent a brief screening for peripheral neuropathy (PN) using a scale of subjective assessment of PN, basic audiometry (hearing impairment), the QTc interval was determined, and visual acuity and color perception (Ishihara color blindness test) were studied [9]. Processing of statistical data was performed with the use of "STATISTICA 6.1» ("StatSoftInc", № AGAR909E415822FA) program. The probability of differences was determined by means of Fisher's ratio test for parametric data. Test statistics is limited to the ratio of sample variance.

RESULTS

The study involved 138 patients, of whom 76 (55.1%) were male-patients and the remaining 62 (45.6%) were female ones. 43 (31.2%) patients were prescribed modified short-term treatment scheme with inclusion for 4 months: bedaquiline (6 months), levofloxacin, clofazimine, ethionamide, ethambutol, isoniazidum (high dose) and pyrazinamide + 5 months of levofloxacin, clofazimine, ethambutol and pyrazinamide; while 95 (68.8%) patients were prescribed individualized long-term treatment regimens. The effectiveness of treatment (see Table I).

Statistical analysis based on Fisher's exact test showed that in patients following individualized regimens of treatment frequent indicators of effectiveness were: treatment

Table I. The treatment effectiveness of patients who received anti-TB agents on a short-term and individualized schemes, %

Treatment effectiveness	Short-term regimens, n=43	Individualized scheme, n=95	P-exact Fisher's test
Treatment interruption	2 (4,7)	9 (9,5)	=0,28
Treatment gap	0 (0,0)	7 (7,4)	=0,0008
Treatment failure	0 (0,0)	8 (8,4)	=0,0007
Cured	39 (90,7)	49 (51,6)	=0,51
Completed treatment	4 (9,3)	18 (18,9)	=0,12
Continue treatment	0 (0,0)	13 (13,7)	=0,0006

Notes: 1) n – number of patients; 2) in parentheses the percentage to the number of patients;
3) p-exact Fisher's test (in comparison with short-term and individualized schemes).

Table II. Adverse reactions in patients following treatment with anti-TB agents on a short-term and individualized schemes, %

Adverse reactions	Short-term regimens, n=43	Individualized scheme, n=95	P-exact Fisher's test
QTcF/electrolyte imbalance	2 (4,7)	6 (6,3)	=0,52
Anemia	2 (4,7)	5 (5,3)	=0,62
Tremor, insomnia, convulsions	0 (0,0)	4 (4,2)	=0,0013
Elevated liver enzymes markers	0 (0,0)	6 (6,3)	=0,0011
Polyneuropathy	3 (6,9)	4 (4,2)	=0,39
Ototoxic effect	0 (0,0)	6 (6,3)	=0,0011
Nephrotoxic effect	0 (0,0)	21 (22,1)	=0,0002
Joint pain	1 (2,3)	7 (7,4)	=0,43
Allergic reaction	0 (0,0)	6 (6,3)	=0,0011

Notes: 1) n – number of patients; 2) in parentheses the percentage to the number of patients;
3) p-exact Fisher's test (in comparison with short-term and individualized schemes).

interruption, treatment gap, treatment failure, completed treatment, continue treatment. In patients following short-term regimens of treatment frequent indicators of effectiveness were: cured, patients did not interrupt treatment, no treatment failure was observed, and they had no need for prolonged treatment.

Adverse reactions on the use of second-line antimycobacterial agents in patients treated with a short-term regimen occurred in 8 (18.6%) cases, while in patients treated with an individualized regimen they occurred in 65 (68.4%) cases (see Table II).

Statistical analysis based on Fisher's exact test showed that in patients following individualized regimens of treatment, frequent adverse reactions were: QTcF/electrolyte imbalance, anemia, joint pain. Polyneuropathy was registered in patients with almost the same frequency, both in the case of a short-term treatment regimen and on an individualized approach. However, adverse reactions such as tremor, insomnia, convulsions, elevated liver enzymes markers, oto-and-nephrotoxicity, and allergic reactions were not observed in patients receiving short-term drug therapy, in contrast to patients treated with individualized regimens.

DISCUSSION

Tuberculosis, despite a thousand-year history of combating it, still remains a leader among highly infectious diseases resulting in high mortality rates worldwide. There is no place on the map where this disease wasn't registered, neither the Great Wall of China nor the Berlin Wall can hold it back. In the process of improving the methods for MTB detecting and treating the disease, Koch's bacillus finds new opportunities to withstand this fierce struggle, often remaining the winner.

The reasons that do not give us the ability to control the TB globally lie in certain features of the pathogen and its adaptive capabilities, the peculiarities of the course of infectious process [10]. The look-back analysis of the problem shows that the only thing that is left of the former familiar disease is its name. Severe clinical forms of the disease, a combination of pulmonary and extrapulmonary localization of the process, co- or polymorbidity of the disease, increasing proportion of risk factors, a sharp increase in the number of drug-resistant TB forms are currently the factors that interfere with the possibilities to take control over the situation [11]. The problem of effective treatment, particularly of such complex forms as chemoresistant TB, remains undeniably important. Thorough analysis of TB treatment barriers makes it possible to divide them into two main points: at the level of a patient and at the health care system level. Speaking about the patient, it involves stigmatization, low level of awareness, disinclination to give up bad habits, long-term treatment, especiallyof chemoresistant TB, and a large number of adverse reactions. [6,12]. Changes in the healthcare system involve approaches to the management of patients with tuberculosis: active use of advanced treatment models with the possibility of video monitoring over the use of medications, reducing the duration of treatment, psychological and financial support. These are the "must have" operational procedures, the use of which will ensure the effective achievement of the ultimate goal – patients' cure [13].

Analyzing the obtained data on the treatment effectiveness in both subgroups of patients, it is possible to state that patients on short-term regimens were 1.8 times more likely to meet the convalescence criteria than the patients from the other group: 39 (90.7%) cases and 49 (51.6%) cases, respectively (p = 0.51). In case of individualized therapy, the incidence of such negative indicators as interruption in treatment was almost two times higher as compared to the modified treatment – 9 (9.5%) and 2 (4.7%), respectively (p=0.28). It is important to note that with the use of short-term treatment regimens, such indicators as interruption of therapy or treatment failure were not observed. Group of patients following the individualized regimen of treatment had a higher percentage of cases of prolonged treatment, as they were regularly prescribed detoxification and pathogenetic therapy due to adverse reactions.

Among the main reasons for the interruption of treatment or treatment gap in TB patients are: deterioration of

health after the start and continuous therapy; unwillingness to take a large number of tablets and injections daily, the need for a long-term hospitalization [12]. The obligatory issue for effective TB management is the control of adverse reactions. And while, QT abnormalities, electrolyte imbalance and anemia in both treatment groups occurred with approximately the same frequency and were slightly pronounced and monitored with the administration of detoxification therapy, the nephro- 21 (22.1%) (p = 0.0002) and ototoxic 6 (6 , 3%) (p = 0.0011) reactions occurred only in the cohort of patients undergoing long-term treatment and were associated with the administration of aminoglycosides. Tremor, insomnia, convulsions, allergic reactions were also the prerogative of patients undergoing individualized treatment regimens.

Certainly, the occurrence of an adverse reaction results in the need to discontinue the basic therapy, detoxify, and sometimes even permanently cancel the drug that has led to this condition. This is a very dangerous tendency: reducing the range of drugs that can be used to arrange treatment – increasing the risk to be transferred to the sad category of palliative care.

CONCLUSIONS

1. The increasing number of resistant strains of MTB has led to the increased number of cases of drug-resistant tuberculosis in Prykarpattia. This fact has a negative influence on both the duration and effectiveness of treatment and imposes a huge economic burden and stigma for the patient.
2. The development and implementation of modified, short-term treatment regimens for chemoresistant tuberculosis will enable the patient to receive treatment at home, reduce the number of drugs used and, consequently reduce the number of adverse reactions.
3. It is critical to follow the patient's roadmap on the timely, early diagnosing of TB cases, especially those caused by resistant strains of MTB; as only an unprovoked patient without resistance to fluoroquinolones can receive this new, effective modified treatment regimen. Therefore, there is another option of diagnostic capabilities that each regional TB center should be provided with – linear probe analysis (LPA) - GenoType MTBDRplus.
4. Constant control over the use of drugs, timely detection of adverse reactions, their prevention and treatment will make it possible to achieve high-quality goals of the patient's treatment.

REFERENCES

1. Feshchenko Yu. I. Suchasni tendentsiyi vyvchennya problem tuberkul'ozu [Up-to-date tendencies in tuberculosis research]. Ukrainian Pulmonology Journal. 2019; 1:8–24. (in Ukrainian)
2. Melnyk V. M., Novozhylova I. A., Matusevych V. G. Prychyny neefektyvnoho likuvannya khvorykh na tuberkul'oz lehen' [Causes of treatment failure in patients with pulmonary tuberculosis]. Ukrainian Pulmonology Journal. 2020; 1:5–9. (in Ukrainian)
3. Lytvynenko N.A., Siomak O.V., Didyk V.S. et al. Pershi rezul'taty kvazieksperymental'noho doslidzhennya shchodo likuvannya rezystentnoho do ryfampitsynu tuberkul'ozu za dopomohoyu skorochenoho povnistyu peroral'noho rezhymu z vykorystannyam novykh preparativ u Zhytomyrs'kiy oblasti, Ukrayina [Preliminary results of a quasi -experimental study of treatment of rifampin -resistant tuberculosis with an all-oral regimen containing new drugs in Zhytomyr oblast, Ukraine]. Tuberculosis, Lung diseases, HIV infection. 2020; 3 (42):17-26. (in Ukrainian)
4. Lytvynenko N.A., Feshchenko Yu.I., Hamazkhina K.O. at al. Pershi rezul'taty vprovadzhennya bedakvilinu dlya khvorykh na mul'tyrezystentnyy tuberkul'oz v Ukrayini: rekomendatsiyi dlya praktychnykh likariv [First results of the introduction of bedaguiline for patients with multidrug resistens tuberculosis in Ukraine: recommendations for practical doctor resume] Tuberculosis, Lung diseases. HIV infection. 2018; 4 (35):19—26. (in Ukrainian)
5. Feshchenko Yu.I., Lytvynenko N.A., Pohrebna M.V. at al. Alhorytm pryznachennya skorochenykh 12-misyachnykh rezhymiv likuvannya na osnovi linezolidu dlya khvorykh na tuberkul'oz z pre-rozshyrenoyu rezystentnistyu MBT. [Algorithm for the use of 12-month linezolid treatments in patients with pre-XDR tuberculosis] Journal of the National Academy of Medical Sciences of Ukraine. 2019; 3:278—284. (in Ukrainian)
6. Aibana O., Dauria E., Kiriazova T. et al. Patients' perspectives of tuberculosis treatment challenges and barriers to treatment adherence in Ukraine: a qualitativestudy. BMJ Open. 2020; 10 (1):e032027. doi: 10.1136/bmjopen-2019- 032027.
7. Lytvynenko N.A., Pohrebna M.V., Sen'ko Yu.O. at al. Alhorytmy pryznachennya skorochenykh 12-misyachnykh rezhymiv likuvannya na osnovi linezolidu dlya khvorykh na mul'tyrezystentnyy tuberkul'oz: pershi obnadiylyvi rezul'taty. [Algorithm of use short 12 month regimens for the linezolid based for patients with multidrug-resistant tuberculosis: first encouraging results] Tuberculosis, Lung diseases, HIV infection. 2018; 3 (34):55—64. (in Ukrainian)
8. Feshchenko Y. I., Zhurilo O. A., Barbova A. I. at al. Vyznachennya profilyu rezystentnosti do protytuberkul'oznykh preparativ v shtamakh m. Tuberculosis, vydilenykh v mezhakh proektu shchodo rozpovsyudzhennya khimiorezystentnykh mikobakteriy tuberkul'ozu v Ukrayini [Determination of m. tuberculosis resistance profile to antituberculosis drugs among the strains, isolated within the framework of the project of m. tuberculosis resistance surveillance in ukraine]. Ukrainian Pulmonology Journal. 2019;1:33–40. (in Ukrainian)
9. Nunn A.J., Phillips P., Meredith S. et al. A trialof a shorter regimen for rifampin-resistant tuberculosis. N. Engl. J. Med. 2019:380 (13):1201—1213. doi: 10.1056/NEJMoa1811867.
10. Todoriko L.D., Petrenko V.I., Denisov O.S. at al. Tyazhki vypadky tuberkul'ozu ta obgruntuvannya shlyakhiv vplyvu na pidvyshchennya efektyvnosti likuvannya za standartnymy skhemamy [Severe cases of tuberculosis and improving the efficiency of treatment in the application of the standard schemes] Tuberculosis, Lung diseases, HIV infection. 2018;2 (33). (in Ukrainian)
11. Todoriko L.D. Imunopatohenez likars'ko-stiykoho tuberkul'ozu z pozytsiy s'ohodennya [Immunopathogenesis of drug-resistant tuberculosis from the standpoint of today] Tuberculosis, Lung diseases, HIV infection. 2017; 3 (30):92—98. (in Ukrainian)
12. Terleyeva Ya.S., Honcharova M.I., Kuzin I.V. et al. Bar"yery likuvannya tuberkul'ozu v Ukrayini [Barriers to TB treatment in Ukraine]. Tuberculosis, Lung diseases, HIV infection. 2020;3 (42):7-16. (in Ukrainian)

13. Kielmann K., Vidal N., Riekstina V. et al. Treatment is of primary importance, and social assistance is secondary: a qualitative study on the organisation of tuberculosis (TB) care and patients' experience of starting and staying on TB treatment in Riga, Latvia. PLoS One. 2018; 13:e0203937. doi: 10.1371/journal.pone.0203937.

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