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RESEARCH ARTICLE

CONFIRMATION OF PRECLINICAL STUDIES DATA ON TIOUREIDOIMINOMETHYLPYRIDINIUM PERCHLORATE (PERCHLOZON) IN CLINIC

Maria Pavlova, Tatiana Vinogradova, *Anna Starshinova, Nadezhda Sapozhnikova, Irina Chernokhaeva and Ludmila Archakovaand Piotr Yablonskii

St. Petersburg Research Institute of Phthisiopulmonology, St. Petersburg

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ABSTRACT

In accordance to international classification Tioureidoiminomethylpyridinium perchlorate (Perchlozon) belongs to thioacetazone group. In vitro Phz demonstrated significant inhibiting effect on viability of drug-resistant mycobacteria strains of TB. In the reported clinical study, which was performed in 2013-2014, 49 patients with MDR lung tuberculosis were enrolled. The patients were divided in two groups: Group I (main) 25 patients were administered Phz in addition to 6 other anti-tuberculosis drugs; in Group II (comparison) 24 patients received 6 anti-tuberculosis drugs. Efficacy of treatment (which was assessed by cessation of bacterial excretion in sputum) was higher in Group I vs. Group II after 3 months (72.4 % (21) vs. 52% (13)) and by 6 months (86.2% (25) vs. 68% (17). Efficacy of treatment with Phz was 72.4% in complex with other anti-tuberculosis drugs.

INTRODUCTION

Tuberculosis, despite the developed strict strategy of infection control and advanced knowledge in epidemiology and mechanisms of survival of the pathogen, is still one of the most common and deadly infectious diseases (Lienhardt *et al.,* 2012; Yablonskii, 2013). For several decades tuberculosis is ranked as one of the controlled infections, but is now becoming a threat on a global scale: more than one third of the world's population is infected with Mycobacterium tuberculosis (MBT), annually TB sick 8.8 million and more than 1.4 million people die from this infection (World Health Organization Global tuberculosis report, 2012, 2013).In recent years, the TB infection control is greatly complicated by the increasing spread of drug resistance TB. According to recent WHO estimates, in the world 3.7% of newly diagnosed patients and 20% of patients who have previously received treatment have MDR-TB. Almost 60% of cases of MDR-TB in the world accounted for India, China, Russian Federation, and South Africa (WHO Global tuberculosis report, 2012).In Russian Federation in the first ten years of XXI century prevalence of tuberculosis is characterized by some stabilization, but it still remains tense due to low level of preventive measures in adults, worsening of clinical forms and increase of the number of smear-positive patients, including multidrug-resistant MBT (Perelman *et al.,* 2003; Sterlikov, 2014). For the period from 2002 to 2012 in Russian Federation the proportion of MDR among all patients with respiratory TB cases has increased twice - from 14.5% to 24.3% (Nizova *et al.,* 2007; Dharmadhikari *et al.,* 2014). The formation of multi-drug resistant strains of mycobacteria, as one of the results of the half-century history of TB treatment, is the main characteristic of tuberculosis (Yablonskii, 2013). Treatment of patients with multi-drug resistant strains requires application of anti-TB second line drugs, which are more toxic and expensive; require longer hospitalization, which, however, often remains inefficient with high levels of morbidity and mortality (Ivanova, 2003).

In this regard, the acute problem is a search for new effective anti-TB drugs to which MBT has retained sensitivity (National Association of TB specialists, 2013). Implementation of new scheme of treatment that can be used against both drug-susceptible TB and MDR-TB is aimed to shorten the length of treatment and decrease mortality from tuberculosis (WHO Global tuberculosis report, 2012). In 1978 – 1988 in St. Petersburg Scientific Research Institute of Phthisiopulmonology more than 1000 compounds with anti-TB activity were screened (TB drugs Perhlozon ® in complex treatment of pulmonary tuberculosis: guidelines, 2013). In Russian Federation for the first time within last forty years in 1993 in Irkutsk Institute of Chemistry PERCHLOZONE®

Corresponding author: Anna Starshinova,
Research Institute of Phthisiopulmonology, St. Petersburg

(Tioureidoiminomethylpyridinium perchlorate; Author's certificate, 1990; Patent RU №1621449, 1993) was synthesized. It belongs to new chemical class of anti-TB drugs of thiosemicarbazone. Required pre-clinical and clinical studies were performed in accordance with standards of GLP and GCP with utilization of laboratories of experimental medicine at Central Research Institute "Institute of Toxicology", Irkutsk (2006) and St. Petersburg Scientific Research Institute of Phthisiopulmonology (2007). Drug demonstrates low toxicity (2.4 times less toxic than isoniazid and 1.9 times than streptomycin), no effect on reproductive function and offspring, moderate embryotoxic effect mainly when administered during organogenesis, with no immunotoxic, carcinogenic, mutagenic properties, as well as no negative effect on immunity, potentiates the activity of phagocytes (Vinogradova *et al.,* 1994; Vinogradova *et al.,* 2007). Perchlozon is low-toxic substance, it does not exert structural-functional abnormalities of vital organs and systems and it does not stimulate gastrointestinal mucosa. In vitro Perchlozon has significant inhibiting effect on viability of drug-resistant mycobacteria strains of TB. Wherein Perchlozon substance ranged from 0.78 to 6.25 mcg/ml.

According to scientists from the National University of Singapore (Thomas Dick, Department of Microbiology and Yong Loo Lin, 2014), the drug has a pronounced effect against drug-resistant strains of mycobacteria (patent by a group of authors RU (11) 2423977 (13) C1) and refers to a pharmacological group of tioatsezazons.Data of III phase clinical study of Perchlozon administration over 3 months in complex therapy of patients with both drug-sensitive and MDR lung TB conducted at the department of pulmonary tuberculosis of Research Institute of Phthisiopulmonology (2010-2012) showed high efficacy of Perchlozon in treatment of patients with pulmonary tuberculosis. However, it is of special interest efficacy of Perchlozon in treatment of patients with MDR TB. In 2012 Perchlozon was registered in Russian Federation for use of TB treatment in routine practice. The reported below study represents experience of Perchlozon (Phz) administration over 6 months in complex anti-TB therapy in patients with MDR lung TB.

Research objective: To evaluate the efficacy of treatment of newly diagnosed cases of MDR lung TB by Perchlozon in complex chemotherapy.

Objective: *To confirm clinical data on efficacy and safety of* Tioureidoiminomethylpyridiniumperchlorate (Perchlozon) in *treatment of MDR lung TB.*

MATERIALS AND METHODS

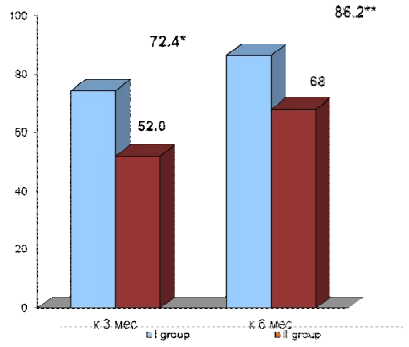
115 patients with initial diagnosis of lung TB were examined in 2013-2014 at St. Petersburg Scientific Research Institute of Phthisiopulmonology by complex laboratory assessment to evaluate drug-resistance of MBT strains. Among 115 patients: in 40 patients (34.8%) drug-sensitive lung TB was diagnosed, while in 75 patients (65.2%) MBT strains demonstrated drug-resistance with XDR profile in 26 patients and MDR – in 49 patients. All 49 patients with MDR were included in the study with 6 months administration of either Perchlozon (Phz) or Levofloxacin (Lfx) in addition to complex therapy with 6 other antituberculosis drugs satisfying inclusion criteria: male and female 18-65 years old; confirmed diagnosis of pulmonary tuberculosis; MDR MBT; signed informed consent on the patient's participation in the study. Efficacy criteria of the study: disappearance of tubercular inflammation by clinical data; culture conversion; regression of X-ray manifestations of tuberculosis (focal, infiltrative, destructive); restored functionality and ability to work. Adverse drug reactions according was diagnosed with Common Terminology Criteria for Adverse Events V.3.0. (17). Among patients completed the study (49 patients): resistance to streptomycin was observed in 81.6% (40) cases, to Ethambutol 59.1% (29), each of the fourth to Ethionamide (22.4%; 11), to Prothionamide in 10,2% (5), to Ofloxacin in 8,1% (4), to Kanamycin in 10.2% (5), to Capreomycin in 8,1% (4), to Pyrazinamide in 6.1% (3). The vast majority of patients were newly diagnosed (93.8%; 46).

Randomization was performed according to the random number generation program (version 14.0) with the distribution of 1:1 into two groups: 25 patients were administered Phz in addition to 6 anti-tuberculosis drugs during 6 months (I group); other 24 patients (II group) were administered Lfx in addition to 6 anti-tuberculosis drugs. After completion of 6 months period patients continued their treatment by 6 anti-tuberculosis drugs only (i.e. without Phz or Lfx). Groups match on clinical, x-ray, and laboratory data. The choice of comparator drug (Lfx) was based on the results of pre-clinical data that suppose its comparative efficacy to Phz.

Complex examination on the study included: clinical (pronounced intoxication syndrome), radiology (multislice computed tomography), and laboratory methods (bronchoalveolar lavage simultaneously investigated RT-PCR (on the basis of a DNA fragment of the gene IS6110) and cultivation in substance Levenshtein-Jensen and BACTEC MGIT960).Statistical analysis was performed using SPSS 16. Chi-square test ($\chi 2$) was used. Risk factor calculation (RR) was under way. Differences were considered significant when $p < 0.05$.

RESULTS AND DISCUSSION

Terms of culture conversion presented in Fig. 1.



** - p< 0.05 in the groups
* - p< 0.001 in the groups

Fig. 1. Terms of bacteriological conversion (%)

Bacteriological conversion was significantly higher in Group I by 3 months of therapy (72.4 % (21) vs. 52% (13)) and by 6 months of therapy (86.2% (25) vs. 68% (17).

X-ray dynamic presented in Fig 2.

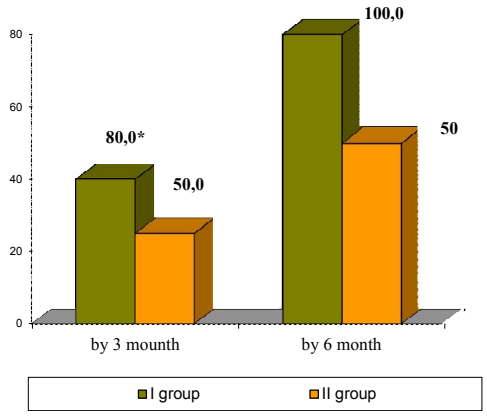


Fig. 2. X-ray dynamics

Positive X-ray dynamics (resorption infiltrative changes, reduction of cavities and closing them) was observed significantly more frequent in Group I by 3 months (40.0% (10) vs. 25.0% (6), $\chi 2 = 7.01$, $p < 0.01$) (Fig.1); and by 6 months: in Group I 80.0% (20) - vs 50.0% (12) in Group II, $\chi 2 = 4.86$; $p < 0.05$ (Fig 2). By 6 months of treatment caverns of disintegration were closed in 68.0% (17) in Group I vs. 41.6% (10) in Group II.

In Group I the most common adverse drug reactions were endocrine disorders (18.4% (9) vs. 0; $p<0.01$) and fever (8.2% (4) vs 0; $p<0.05$) which were not observed in Group II. The opposite: frequency of liver and gastrointestinal tract abnormalities were significantly higher in Group II.

Rates of adverse drug reactions according to organs and systems are presented in Table 1.

Final assessment of efficacy done in 12 months after start of treatment demonstrated that it was higher in Group I (Phz) - (72.4 % (21) vs. 52% (13)).

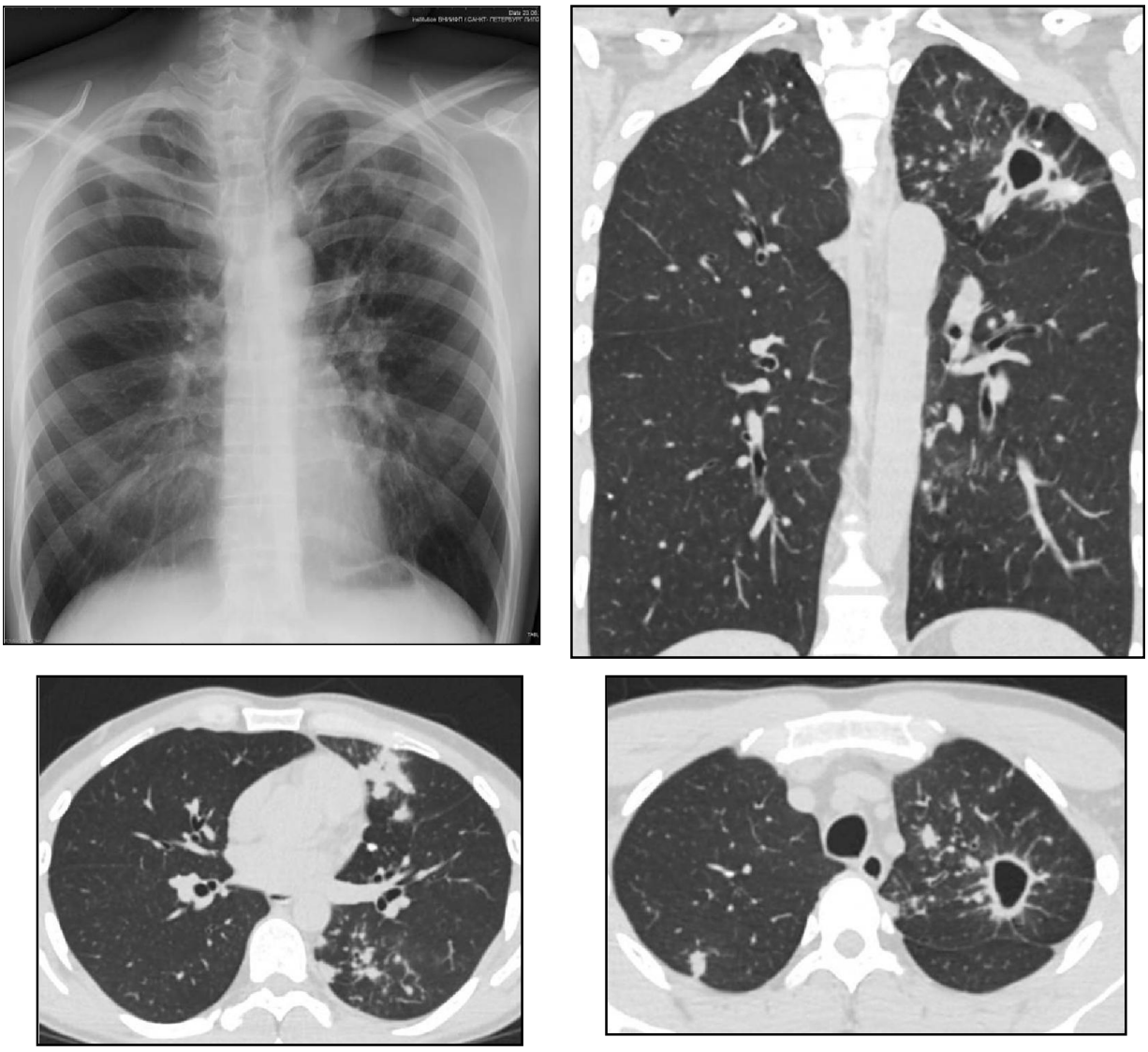


Fig. 3. Clinical example (H., 32) X-ray of patient with MDR-TB in treatment of Perchlozon in 1 month

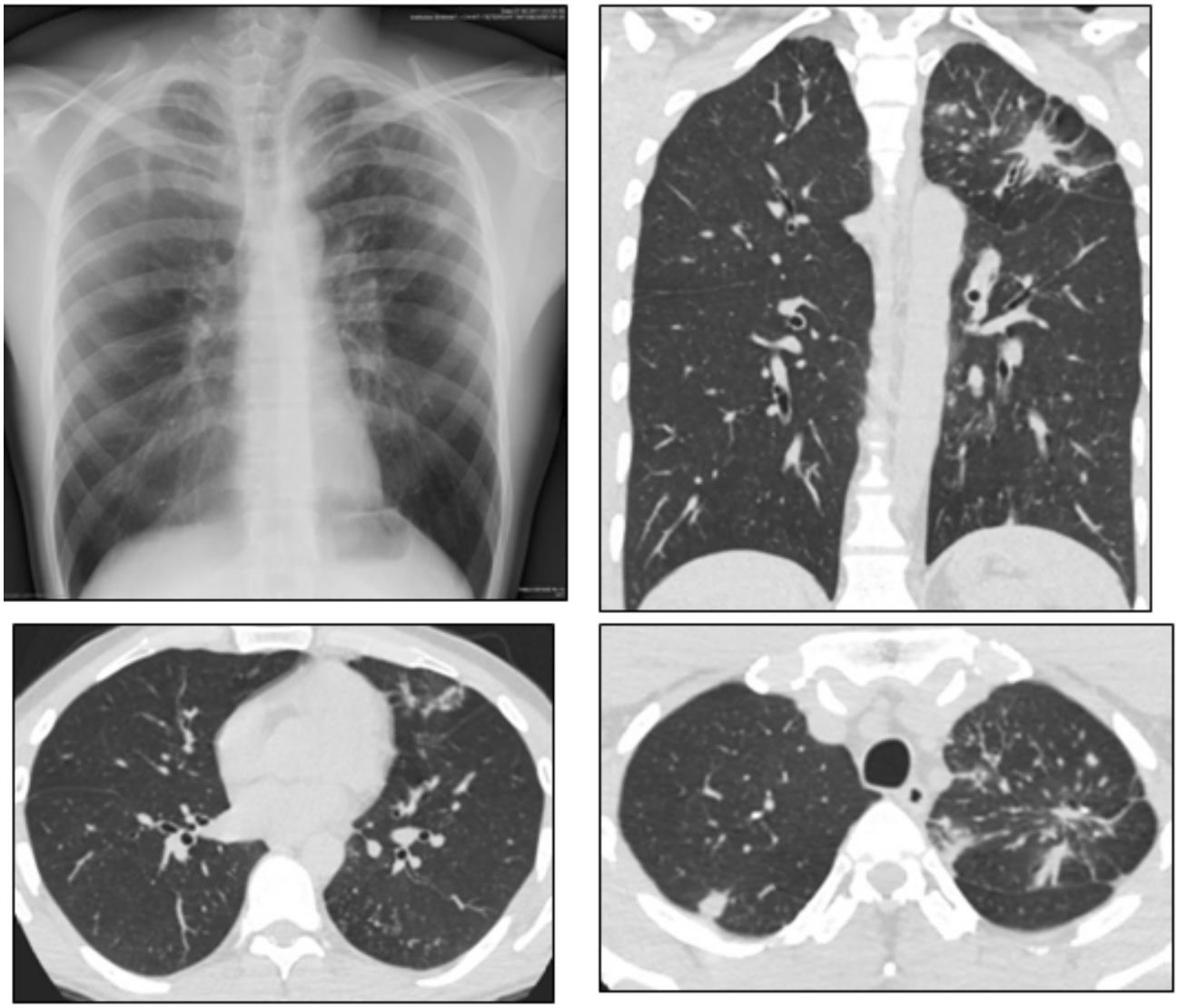


Fig.4 Clinical example. (H., 32) X-ray of patient with MDR-TB in treatment of Perchlozon in 3 month

Table 1.Adverse drug reaction according to organs and systems

	Group I				Group II			
	%/n	RR	x^2	p	%/n	RR	x^2	p
GIT	56.0 14	0.5	0.08	>0.1	62.5 15	0.6	0.08	>0.1
Liver and bile ducts	44.0 11	0.4	1.68	>0.1	60.0 15	0.6	1.68	>0.1
Musculoskeletal damage	32.0 8	0.3	0.16	>0.1	37.5 9	0.4	0.16	>0.1
Endocrine disorders	18.4* 9	0.4	10.58	<0.01	0	0	10.58	<0.01
SKIN and integumentary structures	32.0 8	0.3	0.78	>0.5	20.8 5	0.2	0.78	>0.5
Neurotoxicity	28.0 7	0.3	0.16	>0.1	33.0 8	0.3	0.16	>0.1
Cardiac Toxicity	28.0 7	0.3	0.9	>0.1	16.7 4	0.2	0.9	>0.1
Mental disorder	4.0 1	0.04	0.00087	>0.1	4.0 1	0.04	0,00087	>0.1
Fever	8.2* 4	0.16	4.18	<0.05	0	0	4.18	<0.05

Conclusion

Perchlozone is an new active anti-tuberculous drug effective in treatment of MDR lung TB. Efficacy of treatment with Phz was 72.4% in complex with other anti-tuberculosis drugs.

REFERENCES

Dharmadhikari, A.S.*et al.*2014. Rapid impact of effective treatment on transmission of multidrug-resistant tuberculosis. *Int. J. Tuberc. Lung Dis.,* Vol.18, № 9.- P.1019-1025.

Galkin, V.B. et al., 2013. Status of TB care to the population of the North-West Federal District in 2007-2012, *J. Medical Alliance*; 3 - P. 5-24.

Ivanova, L.A., M.V. Pavlova, L.I. Archakova, 2003. Tactics of treatment of patients with drug-resistant pulmonary tuberculosis, *J. Problems. Tuberculosis and Lung Disease*. - № 5. - C. 14-16.

Lienhardt, C. *et al.* 2012. New drugs for the treatment of tuberculosis: needs, challenges, promise, and prospects for the future, *J. Infect. Dis.* — Vol. 205, suppl. 2. - S. 241-249.

Nizova, A.V. *et al.* 2007. Analysis of drug resistance Mycobacterium tuberculosis with drugs first and second line. - *J. Epidemiology and infection. Disease*, 4.-P.7-11.

Perelman, M.I. *et al.* 2003. Treatment of drug-resistant TB, *J. Antibiotics and chemotherapy*, 8- P. 28-36.

Sterlikov, S.A., 2014. Pulmonary TB patients characteristics and main results of treatment of newly diagnosed registered in 2011, *J. Tuberculosis and Lung Disease*, 7. - P.16-20.

Vinogradova, T. *et al.* 1994. "Perchlozon" - a new compound with high antituberculosis activity. *J. Chemistry of drugs.* - *St. Petersburg*, P.94-95.

Vinogradova, T. *et al.*2007. Evaluating the effectiveness of chemotherapy regimens of drug resistance of experimental tuberculosis. Psihofarma, Biol., Substance abuse, V.7, spec. Issue (Part 1). - P.168.

World Health Organization Global tuberculosis report, 2012.

World Health Organization Global tuberculosis report, 2013.

Yablonskii, P.K. 2013. Russian phthisiopulmonology today - the choice of development path, *J. Medical Alliance*, 3. -P. 5-24.

Yablonsky P.K., 2013. Clinical recommendations for diagnosis and treatment of pulmonary tuberculosis in adults [El. resource]/ edited, National Association of TB specialists.- 48c. - www.naph.ru.

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