MEDICAL AND SOCIAL FACTORS OF RELAPSE DEVELOPMENT IN PATIENTS WITH MULTIDRUG RESISTANT TUBERCULOSIS

Case-control study data of 637 multidrug resistance TB patients, successfully completed treatment course with first line anti-TB drugs plus pyrazinamide, revealed main medical and social factors of the disease recurrence. All patients were treated 4 or 5 months in clinic under standardized directly observed regimes and 18-24 months in out-patient surveillance.

Relapse development was noted in 21 cases and significantly more often appeared in patients living alone and aged 30 to 40 years old.

Keywords: Multidrug resistant tuberculosis, relapses, medical and social factors.

UDC: 616-002.5:579.252.55]-02-036.-87-058

Introduction

The prevalence of tuberculosis with multidrug resistance (MDR TB) induces the great anxiety (WHO, 2007; WHO, 2004). In 2008 MDR TB incidence constituted 8.5 per 100,000 in Kazakhstan (Ismailov, 2009).

One of the correct approaches to resolve the problem of growing and spreading drug resistance associated with anti-epidemiological and anti-TB activities is the implementation of the alternative courses of chemotherapy with anti-TB drugs of the second line (Partners in Health, 2002; Mishin, 2008). The term “DOTS-Plus” firstly was sounded by WHO in 1998 that allowed to pay attention to the need in elaboration and implementation of the program on strategy and tactics of MDR TB management in the countries with high burden of tuberculosis. In 2000 the Working Group of WHO developed and published the first “Guidelines for the programmatic management of drug-resistant tuberculosis (WHO, 2008).

The experience of different international projects, in particular in the countries of CIS, showed the high effectiveness of DOTD-Plus Strategy in the fight against tuberculosis (Zignol et al., 2005). Since 1999 in Kazakhstan there has been implemented the pilot projects of the Programme DOTS-Plus on the base of WHO recommendations, and since 2003 all the country was covered by this Programme. Up-to-day 7153 patients completed the treatment by this regimen. At this, indicator of cure constituted 82.2% (Ismailov, 2003).

At present stage of DOTS strategy management investigation of relapse development in patients with MDR TB earlier successfully treated by chemotherapy with anti-TB drugs of the first and the second lines is of a great interest.

Thus, by data of Migliory et al. (2002) out of 18 patients with MDR TB successfully completed the treatment with anti-TB drugs of the first line, relapse of TB disease was revealed in 5 (27.8%), at this, the middle time of relapse emergence constituted 10.4 ±10.7 months. Along with, by data of other authors (Mukherjee et al., 2004, 2006), percentage of TB relapse development in patients with MDR TB, after adequate directly observed treatment conducted, constituted 5% of cases. At this, in the majority of those patients, at implementing the drugs of the second line, amplification of resistance specter did not occur. As a result, authors concluded that the reasons of relapse development were discrete but viable bacteria hidden in a cavity or into fibrous tissues where penetration of anti-TB drugs was not possible.

The preliminary data of the National Center for TB Problems (Kazakhstan), indicate to the lower percentage of relapse development in patients with MDR TB after
chemotherapy conducted under regimen DOTS-Plus, i.e. 3.2% of cases (Berikova and Zhaparkulova, 2010).

Unfortunately, literature sources based on the evident data of study of the cohort analysis of MDR TB relapse cases registered in patients treated under regimen DOTS-Plus are poor. Apparently, at present absence of the international consensus and data on effective and economically possible implementation of the strategies of MDR TB patients treatment gives to the national tuberculosis programs the difficult choice to determine the unified indicators of patients registration and definitions of treatment outcomes (Laserson et al., 2005).

In the clinical practice of the last years the summarized term “reactivation” was used to include both the notions of “exacerbation” and “relapse” (Kolomijetz, 1982; Kovalenko, 1989). Further, division of the notions of “exacerbation” and “relapse” occurred. At this, it was implied under “exacerbation” TB process outbreak after effectively treatment completed before clinical cure statement, while “relapse” meant TB process outbreak in persons treated earlier with outcome “cured”.

Since a moment of implementation of the program of management of the patients with MDR TB introduction of the special terminology was foreseen to be used in the new classification of TB cases depended on nature of TB bacilli excretion and treatment outcomes. At this well known in the past notions such as TB disease exacerbation, early and late TB relapses were not foreseen to be used in the phthisiatric practice up-to-day.

At present under term “category IY, “relapse” there are implied the patients earlier treated with anti-TB drugs of the first or second line with outcome “cured” or “treatment completed” and at this moment they have the bacteriologically confirmed M. tuberculosis emission (MHRK, 2008). Without a doubt, positive sputum smear is the main sign of the clinical activity of TB process. But it should bear in mind whether it is the consequence of the reactivation of TB process in a patient or the sign of main course of chemotherapy uncompleted up to end, i.e., statement of a “pseudo-relapse”.

Thus, analysis of literature data is of evidence that the clarification of the questions of relapse development in patients with MDR TB earlier treated under DOTS-Plus regimen is insufficient, namely, reasons of relapses emergence, treatment tactics, united approaches to the unified definition of the notion “relapse”. In the present stage of DOTS-Plus strategy management study of the reasons of relapse emergence in patients with MDR TB successfully treated earlier with course of chemotherapy with anti-TB drugs of the first and second line is of the great interest.

Aim of this study is the investigation of cause of relapse development in patients with MDR TB treated under regimen DOTS-Plus.

**Material and methods**

Design of the study: cohort investigation. Population to be investigated: 637 patients with TB. Depending on presence or absence of disease relapse after successful completion of all administrated 18 to 24 month’ treatment course with anti-TB drugs of the second line (DSL) with outcome “cured” all analyzed groups of patients was divided in two subgroups.

The main group was constituted from 21 patients, which were treated at the Department of Pulmonary TB of the National Center for TB Problems under standardized regimen with DSL with outcome “cured” over period of 2000-2004. During following years of observation from 4 to 8 years TB disease relapses developed. The control group included 616 patients successfully treated with DSL at the same period, and no in the follow-up period of observation relapses were registered among them.

Relapses are designed by us as patients with MDR TB earlier treated under standardized regimen with drugs of the first or second line with outcome “cured” or “treatment completed”, and during follow-up period of observation they were stated the clinical and roentgenological activity of TB disease with positive sputum smear confirmed
bacterioscopically and by culturing and without it. All the patients were received the treatment with DSL in the standardized regimens under direct observation during 4 to 5 months in-patient, then it did out-patient during 18 to 24 months. The treatment consisted from 2 phases: intensive and continuation ones. In the intensive phase patients received the capreomycin or amikacin i/m, prothionamid or ethionamid, ofloxacins (levofloxacins, cycloserin, pyrazinamide and ethambutol when M. tuberculosis sensitivity kept per os from 4 months or more. This treatment phase was conducted under clinical conditions. The continuation phase with thioamide, ofloxacin (cycloserin) was implemented under clinical conditions. The durability of the complete chemotherapy course was 18-24 months depending on the heaviness of the primary specific process.

Patients were under strictly observation of the nurses, physicians and Head of the Department. Before treatment beginning conversation with each patient on disease management under strict observation, evaluation and classification of routine problems was conducted. During each visit of a physician question about adverse reactions was put to the patients, and their responses were fixed in the disease histories and out-patient or medical cards. Before to be included in our study each patient was underwent to the complete clinical examination. The main laboratory analysis included the bacterioscopy and smear sputum culturing with drug sensitivity testing (DST) for anti-TB drugs of the first and the second lines, the complete blood account, general urine account, biochemical analysis, blood’ urea, serum creatinine level, liver function tests (transaminases, serum bilirubin levels) which were conducted monthly. Before MDR TB therapy there were conducted the roentgenotomographic investigations. It was elaborated and analyzed the individual card for patients from these groups.

For statistical processing of our data obtained we used the program SPSS for Windows version 16.0 (Chicago, USA). To determine the significant factors influenced on TB relapse development it was used the statistical test $\chi^2$. Results were evaluated by criteria as following: if at accounting the unit did not exceed the limits of 95% of the confident interval, the difference was considered as statistically reliable.

We elaborated the individual card for observation of a patient. The card included the passport party, clinical diagnosis, concomitant diagnosis, complications, objective status of a patient, data of instrumental and laboratory methods of investigations. In particular, data of sputum bacterioscopy for MBT, roentgenological data at hospitalization and in dynamics were to be given.

As the criteria for treatment effectiveness evaluation there were chosen the results of microscopy and culture, clinical and roentgenological data and treatment outcomes.

**Results and discussion**

Comparative evaluation of medical and biological signs in the main and control groups was performed by us. In the Figure 1 it is presented the distribution of patients analyzed by gender.

As it is seen in the figure 1, in both groups males among patients were prevalent. So, in the main group 13 (62%) were males, 8 (38%) females, and in the control one 337 (55%) were males and 279 (45%) females respectively.

More than a half of patients in the main group 11 (52.3%) were persons of the age group from 30 to 39 years. In the control group patients of the younger age up to 29 years were prevalent: 341 (55.3%) versus 6 (28.6%) patients in the main group of the same age. Percentage of patients of 40 years and older in both groups was virtually equal. The distribution of patients by age categories is presented in the Figure 2.

At evaluating the family status of the analyzed groups it was stated that more than a half of patients (57.1%) in the main group versus 47.6% in the control one did not have a family. Percentage of patients (33.3%) having a permanent job in the main group was reliably higher that in the control one (14.8%). From patients jobless in both groups in the
majority of cases patients were invalids by reason of tuberculosis (38.1 and 44.5% respectively).

In both groups patients with fibrocavernous pulmonary tuberculosis (66.7% and 75.0% of cases respectively). Percentage of patients with infiltrative tuberculosis in the main group constituted 33.3% of cases versus 22.4% of cases in the control one. In remained 2.6% of cases in the control group other TB forms were diagnosed.

In all patients of both groups there were marked the different complications of the main disease. At this, all patients of the groups to be compared suffered from cardiorespiratory insufficiency of different degrees. Lung hemorrhage and hemoptysis were observed in 10.5% of cases in the main group and in 18.2% of the control one. By frequency of complications in the groups of comparison and by their varieties it did not reveal any statistically reliable difference.

Percentage of different concomitant diseases in the groups of comparison was the same (by 33.3% of cases). In both groups of comparison pathology of gastrointestinal tract was marked the most frequently (42.9% versus 21.4% respectively). At this patients in which there were observed the TB relapses in the follow-up period reliably more frequently suffered from gastrointestinal diseases (GD).

Diabetes mellitus was observed in 3 (14.3%) patients of the main group and in 30 (4.9%) patients of the control one. No there were revealed by us any statistically reliable difference in the frequency of diabetes mellitus in the groups of comparison. The chronic obstructive pulmonary diseases (COPD) were observed in 7 (1.1%) of cases in the control group. In the main group this pathology was absent.

Along with, 2 (9.5%) patients of the main group and 20 (3.3%) patients of the control one were alcohol abusers. One (4.8%) patient from the main group and 12 (2.0%) patients...
from the control one were drugs abusers. The patients of both groups did not reliably differ by presence of harm habits.

The confinement anamnestic was present in 1 (4.8%) of the main group and 58 (9.4%) of the control one. So, no patients of the control group had statistically reliable frequency of confinement in anamnestic. In general contrary to the well recognized opinion presence of harm habits and confinement in past did not influenced on the frequency of relapse development in patients successfully completed the treatment course with anti-TB drugs of the second line.

At hospitalization to the department the health status of the majority of patients analyzed was evaluated to be of the middle heaviness (47.6% and 47.4% of cases respectively). In the department there were hospitalized 7 (33.3%) patients from the main group and 270 (43.8%) from the control one in the sufficient status. The heavy status was marked reliably more frequently in the main group (19.1%) by comparison with the control group (9.3%). The adverse reactions for DSL were marked with nearly same frequency in both groups compared (79.9% and 71.4%) respectively) that is seen in the Figure 3.

**Figure 3. Frequency of adverse reactions (AR) on anti-TB drugs of the second line**

At this, no eliminable adverse reaction for DSL were observed more frequently in the main group (14.3% of cases). In the control group non-eliminable adverse reactions for DSL were marked statistically reliably in 4.9% of cases.

Thus, such variable as the age of patients (30-40 years), solitude, patient heavy status at their hospitalization in the department, presence of concomitant gastrointestinal diseases and adverse reactions to anti-TB DSL of non-eliminable nature had the reliable significance, independently on one another, for relapse development after successfully completion of all treatment courses.

**Conclusion**

On the base of analytical investigation (case-control study) of data for 637 patients with tuberculosis with multidrug resistance completed successfully the treatment course with anti-TB drugs of the second line in combination with pyrazinamide we stated the main medical and social factors of relapse development.

All patients were treated under direct observation with DSL drugs by standardized regimens during 4-5 months in clinic, then 18-24 months out-patient. The treatment was constituted from 2 phases: intensive and continuation phases. In the intensive phase patients received the capreomycin or amikacin i/m, prothionamid or ethionamid, ofloxacin (levofoxacin), cycloserin, pyrazinamide and ethambutol at sensitivity kept of MDT to it per os during 4 or more months. This phase of treatment was conducted under clinical conditions. The continuation phase with thionamides, ofloxacin (levofoxacin), cycloserin was implemented out-patient. In further, out of 637 patients completed
successfully the all treatment course, TB disease relapses were stated in 21 cases. The frequency of relapse development among patients with MDR TB constituted 3.3%.

The relapse developed reliably more frequent in patients in the age up to 30 - 40 years, living without family. The study has considered such medical factors influenced to TB relapse development as the heaviness of patient' status before treatment course beginning, gastrointestinal diseases and non-eliminable adverse reactions to one or two anti-TB drugs of the second line.

In connection with this, for preventing MDR TB relapses in patients successfully completed the treatment course with anti-TB drugs of the second line, in the practical medicine it is necessary to give the timely diagnosis and comprehensive treatment of GI diseases, and, also, timely eliminate the adverse reactions to anti-TB drugs avoiding their cancellation.

References


Ismailov, Sh., 2009. “Statistical review on tuberculosis in the Republic of Kazakhstan” [Statisticheskiy obzor po tuberkulozu v Respublike Kazakhstan], in Russian, Almaty.


