

Latent Tuberculosis Infection, Possibilities of Diagnosis and Treatment in Patients with HIV Infection

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Abstract

The review presents domestic and foreign literature data on current issues of latent tuberculosis infection (LTBI) and its role in the risk of developing tuberculosis in different population groups, including patients with HIV infection. It has been shown that the greatest risk of developing tuberculosis in persons with LTBI occurs with HIV infection: the annual risk of developing tuberculosis increases by 10%. In the diagnosis of latent tuberculosis infection, allergic skin tests (Mantoux and Diaskintest test), detection of MBT antigens (PCR) and antibodies (ELISA) and in vitro tests based on the production of γ -interferon under the action of various MBT antigens are currently used in the Russian Federation. Based on the results obtained, the tactics and treatment regimen for LTBI were determined. The review presents the main information obtained by domestic and foreign researchers on the results of LTBI treatment to reduce the risk of developing tuberculosis in HIV-infected patients. The article discusses topical issues of chemoprophylaxis of tuberculosis in HIV patients with LTBI, which presents effective treatment regimens aimed at reducing the risk of reactivation of tuberculosis infection, reducing the drug load on the patient and the development of adverse reactions.

The acquisition of new knowledge on the LTBI problem will contribute to the solution of an important task - control over the progression of tuberculosis in HIV-infected patients.

Keywords: *Latent Tuberculosis Infection; Chemoprophylaxis; Allergic Skin Tests; Combined Tuberculosis; HIV Infection; LTBI Treatment*

Introduction

According to WHO, a third of the world's population is infected with mycobacterium tuberculosis (MBT), but there is no exact data on how many of them will get sick with tuberculosis. Thus, it can be concluded that one third of the population has latent tuberculosis infection (LTBI) [1].

LTBI, according to most phthisiatricians, is MBT infection without clinical, radiological, bacteriological and morphological data. According to the Federal Clinical Guidelines for the Diagnosis and Treatment of LTBI and CDC (Center for Disease Control and Prevention, USA), this is a state of a persistent immune response to MBT antigens in the absence of clinical manifestations of active tuberculosis. It should be noted that LTI problems have been discussed for over a century. Many researchers believed that such an infection, caused either by a small amount of MBT penetrated into the body, or by their weak virulence, develops most often in people susceptible to tuberculosis [2-5].

Pathogenesis of LTBI: The likelihood of infection in patients excreting MBT with sputum (by the method of bacterioscopy) is the main source of the disease, however, patients with negative results of sputum smear examination for the presence of MBT also pose a certain danger: Dried droplets of sputum (the so-called droplet nucleoli) retain the virulent pathogen for a long time. Accordingly, the probability of infection is determined by the degree of danger of the source of infection, as well as the closeness and duration of contact [6]. The work of recent years, carried out with the help of molecular technologies, has revealed an increased role in the occurrence of tuberculosis of endogenous infection.

It should be noted that LTBI patients are not contagious until MBT reactivation begins [7].

The degree of danger of the source of infection and the risk group for LTBI.

The highest rates of infection (or LTBI) occur in cases of family contact with patients excreting MBT. A classic example is the spread of tuberculosis on one of the US submarines. A turn of tuberculin reactions as a result of contact with a patient with cavernous pulmonary tuberculosis occurred in 80% of the sailors who were in the same compartment of the submarine, and only in 54% of the other compartments. The risk group for MBT infection includes children under 5 years of age, children in contact with adults, medical workers, primarily employees of bacteriological laboratories, employees of shelters for the elderly and homeless. In addition, patients with HIV infection, neoplasms, chronic renal failure, late-stage diabetes, as well as people receiving immunosuppressive therapy and organ transplantation [8-10].

The "maturity" of the microorganism: The degree of "maturity" of MBT strains is determined by its ability to survive and reproduce in the host organism. According to a number of authors [11], MBT strains resistant to PTP, in particular to isoniazid, have reduced virulence for laboratory animals. It is quite probable that they are less virulent for humans, but there is no information that they are not able to cause LTBI, which is absolutely relevant in the modern period of the spread of MDR MBT.

The role of the massiveness of the infection and the likelihood of developing tuberculosis after infection: According to the literature, in persons with a positive Mantoux test (without other risk factors), the probability of developing active tuberculosis is about 0.1% per year [12]. The risk of both infection with tuberculosis and the development of an active process is greatest in contact with patients in whose sputum MBT is detected by the method bacterioscopy. Thus, the probability of the disease in such cases is 8 - 10 times higher than in contact with patients, in whose sputum the pathogen is detected only by the culture method and 16 - 20 times higher than in contact with an acylated patient. The cumulative risk of developing tuberculosis is 5% in the first 5 years after MBT infection and does not exceed 5% throughout subsequent life.

The role of age and geopolitical factors: The highest incidence of tuberculosis is found in children under the age of 3 years after the turn of tuberculin reactions. This is due to recent infection and the high susceptibility of young children. Countries with low tuberculosis epidemics are considered to have the highest number of persons with LTBI (0.3%), regardless of BCG vaccination. In countries "intermediate" in relation to the tuberculosis epidemic, the number of such cases of the population is less than 4% and it increases to 20% among patients who have been in contact with patients with tuberculosis - bacterial excretors. In regions with a high tuberculosis epidemic, the number of LTBI cases reaches 30% and increases to 60-70% with domestic contacts [13].

The role of immunosuppression: The immune system in 90% of all infected persons is able to suppress MBT throughout their lives. However, this ability is lost when the immune system is suppressed as a result of disease. The greatest risk of LTBI progression and development of tuberculosis occurs with HIV infection: approximately 10% and each year the risk of developing tuberculosis increases by 10% [14]. The rate at which the possibility of developing tuberculosis increases with seroconversion (an increase in the antigenic load in patients with HIV infection) is very high - during the first two years of "a critical decrease in CD4+ [15]. Therefore, the selection among the contingents of persons at high risk of tuberculosis and their preventive treatment is the most important task of controlling this disease.

LTBI diagnosis: Currently, 4 main methods of LTBI diagnostics are used in Russia: detection of MBT antigens (PCR), detection of anti-tuberculosis antibodies (ELISA), *in vitro* tests (IGRA tests) and skin tests (tuberculin diagnostics - Mantoux and Diaskintest test). There are mainly 3 types of tuberculin used in the world: Danish PPD-RT23 (in most countries), American PPD-S and Russian PPD-L, made from 2 strains (humanus and bovis) and it has not been compared with other tuberculins [16]. However, according to 14 meta-analyses of foreign studies, the cumulative sensitivity of the tuberculin test was 71%, which indicates a low predictive value of the Mantoux test for the diagnosis of LTBI [17,18].

IGRA tests *in vitro*: Quantiferon TB and T-SPOT, as well as the Russian test with recombinant tuberculosis allergen (ATP) (Diaskintest drug), which was an analogue of the IGRA tests [19], have a high predictive value in the diagnosis of LTBI. All of them are recommended for use in the Russian Federation [20]. It should be noted that the cost of 1 dose of ATP is less than 1.5 euros, while the cost of consumables alone for one Quantiferon TB study is 40 euros. Therefore, the ATP test in Russia is used for mass screening of LTBI, which also showed high sensitivity (more than 95%) during a continuous examination of patients identified in 2012 - 2014 [21,22]. In the study [23], it was shown that the positive sensitivity of the Diaskintest test in patients with HIV infection, as the most difficult group of patients for LTBI diagnosis, ranges from 30% to 40%, which undoubtedly plays a large role in the comprehensive examination of this category of patients.

It should be noted that in patients with HIV infection (at the AIDS stage), when the number of CD4+ T lymphocytes decreases significantly in a significant number of cases, the immune response is suppressed and cannot both active tuberculosis infection and LTBI can be detected. Due to the fact that in recent years there has been a significant increase in patients with HIV infection and, accordingly, a high risk of LTBI reactivation, diagnosis and its treatment are becoming an important method of combating tuberculosis in this group of patients.

LTBI treatment and modern approaches to chemoprophylaxis: The decision to treat LTBI should be made on an individual basis, based on a full assessment of the risk of developing active tuberculosis. According to a number of researchers, over 50% of all HIV-infected people fall ill with tuberculosis throughout their lives, and in 40% of these cases, active tuberculosis occurs in the first 5 months of the disease. Prescribing anti-TB drugs to people at low risk of developing TB is more likely to result in adverse reactions rather than reducing the risk of an active process. The detection of LTBI among the contingents most at risk of the disease, in particular, HIV-infected patients, serves as an indication for the appointment of prophylactic chemotherapy [24]. As a result of numerous studies, preventive therapy (chemoprophylaxis) in persons with LTBI significantly reduces the risk of developing active tuberculosis in them, especially in the group of patients with HIV infection. However, according to [25,26], the coverage of tuberculosis chemoprophylaxis among HIV-infected patients in the Russian Federation in 2017 remains at a low level - 23.8% among newly diagnosed HIV-infected patients and 16.4% among patients registered with AIDS centers, which undoubtedly affects the general epidemic situation of HIV/tuberculosis co-infection.

The effectiveness of chemoprevention of tuberculosis in patients with LTBI: After experimental and extensive clinical studies, which proved the high efficacy of isoniazid for the chemoprophylaxis of tuberculosis, this drug was recommended for the treatment of LTBI. The effectiveness of such treatment ranges from 25% to 92% (in on average, about 60%), which depends on the accuracy, completeness and controllability of the therapy [27]. Thus, the incidence of tuberculosis decreased by 93% among people without HIV infection who took at least 70 - 80% of their prescribed doses of isoniazid during 12 months of treatment. It should be noted that a similar effect was traced during 19 years of observation and it is likely that it will persist throughout the life of patients. However, in patients with HIV infection, the greatest effect is observed with the use of combined chemotherapy (2 anti-tuberculosis drugs (anti-TB drugs) for 3 - 6 months, which lengthens the protection by 2.5 - 3 years. Thus, a comparison of the effectiveness of preventive treatment with one anti-TB drug (isoniazid) and 2 (isoniazid + rifampicin) in HIV patients in Africa showed a pronounced advantage of the second regimen, since tuberculosis developed after 10 months of observation in 3.7% of patients in the first group and 1% in the second group. However, after 36 months, the results were the same in both groups (got tuberculosis 5.4% and 5.3%, respectively.) The effect of the administration of rifampicin alone for LTBI has not been carried out in controlled trials, although the high efficacy of this regimen has been confirmed in the treatment

of LTBI caused by MBT infection resistant to isoniazid. rifampicin accelerates the clearance of many drugs, weakening their effect, the use of rifabutin is preferable in this regard.

Possibility of developing drug resistance (DR) during LTBI treatment: The development of LU MBT during LTBI treatment seems unlikely due to the small number of MBT, which is in a latent, dormant state.

Chemoprophylaxis of tuberculosis should be carried out with caution when:

1. Chronic liver diseases in the stage of decompensated cirrhosis (class B and C on the Child-Pugh scale);
2. Chronic kidney disease 4 - 5 stages (for regimens with rifampicin);
3. Diseases of the central nervous system with epileptic syndrome.

In chronic liver diseases in the stage of decompensated cirrhosis (class B and C on the Child-Pugh scale), the question of the appointment of chemoprophylaxis and the therapy regimen is decided by a council of doctors consisting of: phthisiatrician, hepatologist, infectious disease specialist. Rifampicin, rifabutin and rifampentin are contraindicated in stage 4 - 5 renal failure. In diseases of the central nervous system with epileptic syndrome, isoniazid is contraindicated.

The patient is given drugs for prophylactic treatment in accordance with the schedule of visits to receive ART. It is necessary to have feedback from the patient (during the first month of chemoprophylaxis at least once every 10 - 14 days, then at least once a month) for the timely assessment of the development of adverse events associated with the drugs taken and adherence to therapy.

Currently, in the Russian Federation, chemoprophylaxis of tuberculosis is carried out on the basis of the "Instructions for chemoprophylaxis of tuberculosis in adult patients with HIV infection" dated 03/14/2016 based on the data of clinical and radiological studies and the results of Diaskintest.

A patient with HIV infection can be assigned one of the regimens of chemoprophylaxis of tuberculosis, comparable in effectiveness and safety:

1. Isoniazid (5 mg/kg) and vitamin B6 (15 - 25 mg/day) - 6 months;
2. Isoniazid (5 mg/kg) and vitamin B6 (15 - 25 mg/day) + rifampicin (10 mg/kg) or rifabutin (5 mg/kg) - 3 months;
3. Isoniazid 900 mg and vitamin B6 (15 - 25 mg/day) + rifapentine 900 mg (for a patient weighing more than 50 kg) once a week for three months.

Recommended doses of drugs for the third CP regimen: isoniazid: 15 mg/kg; rifapentine (by body weight): 10.0 - 14.0 kg = 300 mg; 14.1 - 25.0 kg = 450 mg; 25.1 - 32.0 kg = 600 mg; 32.1 - 49.9 kg = 750 mg; > 50.0 kg = 900 mg. The chemoprophylaxis regimen, which includes isoniazid and rifapentine, should be carried out under the direct supervision of medical personnel (supervised chemoprophylaxis of tuberculosis). The drug rifapentine as part of a chemoprophylaxis regimen can only be used in HIV patients who are not receiving ART, since rifapentine is contraindicated in therapy with HIV protease inhibitors and non-nuclease HIV reverse transcriptase inhibitors. As a rule, this is a group of patients who were in close contact with tuberculosis patients with CD4 + more than 350 cells.

In case of contraindications to the appointment of rifampicin, rifabutin, rifampentin, alternative treatment regimens are the appointment of combined anti-tuberculosis drugs phthisopyram (isoniazid (5 mg/kg) and vitamin B6 (15 - 25 mg/day) + pyrazinamide (25 mg/kg) - 3 months and phthyoetam) (isoniazid (5 mg/kg) and vitamin B6 (15 - 25 mg/day) + ethambutol (15 mg/kg) - 3 months.

The duration of chemoprophylaxis for tuberculosis should be increased if a patient with HIV infection continues to be in the focus of tuberculosis infection for the duration of the outbreak or is in prison, where chemoprophylaxis with isoniazid should preferably be carried out for 36 months (due to the high incidence rate and the possible risk of contact with a patient with tuberculosis).

When carrying out chemoprophylaxis of tuberculosis, it is necessary to monitor the functional state of the liver (the level of aminotransferases, total bilirubin) 1 month after the start of chemoprophylaxis of tuberculosis and then once every 3 months with isoniazid monotherapy, and once a month with a combined regimen of preventive treatment. With an initially elevated level of aminotransferases, the first study of a biochemical blood test should be carried out 2 weeks after the start of chemoprophylaxis and monthly thereafter. The main criterion of effectiveness chemoprophylaxis of tuberculosis is the absence of cases of development of active tuberculosis in persons who have received chemoprophylaxis of tuberculosis during the next 2 years. If, 1 year after the prophylactic course, the number of CD4 + lymphocytes in the patient does not exceed 350 cells per μl , the chemoprophylaxis of tuberculosis should be repeated annually, regardless of antiretroviral therapy, until the CD4 count is above 350 cells per μl .

In 2014, the WHO Global Strategy to End the Global Tuberculosis Epidemic was published, according to which a 90% reduction in new cases should be achieved between 2015 and 2035. By 2035, none of the families with tuberculosis patients should have to bear the cost of providing preventive treatment by 2035. their reception, the issue of reducing the duration of therapy, reducing the number of pills used and increasing patient adherence to treatment remains highly relevant at the present time. In this regard, the scheme of chemoprophylaxis of tuberculosis in patients with HIV infection using rifapentine + isoniazid, when a patient with HIV infection takes drugs once a week, is strategically important in practical terms.

The drug rifapentine is a derivative of rifamycin, an antibiotic produced by *Amycolatopsis mediterranei* and is the most widely used for the treatment of tuberculosis. No cross-resistance has been observed between rifapentine and other anti-TB drugs. However, one of the main advantages of rifapentine is a longer elimination period of the drug - 4-5 times longer than that of other rifamycins - which allows it to be used in intermittent LTBI treatment regimen [28]. For almost 20 years of use of the drug, the safety and efficacy of rifapentine has been demonstrated both in clinical practice and in a number of randomized and non-randomized clinical trials [29].

In 2010, the European Medical Agency granted rifapentine the status of an orphan drug, and in 2011 rifapentine in combination with isoniazid was recommended in the United States as an alternative treatment regimen for latent tuberculosis infection (LTBI), even in children aged 12 years and older. In November 2014, the FDA approved an additional indication for the use of rifapentine: use for the treatment of LTBI in combination with isoniazid in patients aged 2 years and older with a high risk of TB progression. A WHO expert committee has recommended that rifapentine be added to the list of essential medicines. Studies have shown that rifapentine was well tolerated in the group of HIV-infected patients; all adverse events recorded during the study were of moderate intensity.

Conclusion

Cost-effectiveness of chemoprophylaxis of tuberculosis. The studies have shown that the economic efficiency of chemoprophylaxis of tuberculosis among HIV-infected patients has a significant benefit for the budget in comparison with the cost of treating patients with HIV-associated tuberculosis by 67.7% per year.

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