The prevention of herpes-viral infections with interferon therapy in combined treatment of pulmonary tuberculosis

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Abstract. The rationale for immunotherapy with interferon -α-2β (VIFERON® 3 million IU and 1 million IU in suppositories) in the treatment of pulmonary tuberculosis in adolescents was the prevalence of clinical and laboratory markers of secondary immune deficiency identified complex examination 62 hospitalized patients: more than two chronic diseases (75,8%); recurrent infection caused by the herpes simplex viruses (HSV 1,2) (54.8 %), on the background of combined serological HSV 1,2activation (90.3 %) and cytomegalovirus (CMV) infection (93.6 %); the decrease in the absolute number of leukocytes and the low levels orabsence of interferon -alpha (29.0 %) and interferon - gamma (77.4 %). The efficiency and safety of the treatment with VIFERON® proved on the basis of significant positive clinical and laboratory criteria: an increase in body weight in 84.6 % of adolescents; reducing the frequency of arrhythmias; increase in absolute lymphocyte count (46.1%); decreased serological activation HSV 1,2 (30.8%) and CMV (61.5 %); increase in the amount of interferon -alpha (61.5 %) and interferon - gamma (61.5 %);the absence of the intolerance 3 times reduction in the undesirable effects of chemotherapy.
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Introduction

Tuberculosis remains one of the most topical medical, biological and socio-economic challenges facing the world community [1, 2, 3]. Russia is among the 22 countries with the highest burden of tuberculosis [3]. Moreover, if the morbidity of the permanent population of Russia reduced by 13.5% (from 66.6 to 57.6 to 100 000 population) from 2002 to 2012 and that in the case of adolescents has not changed - 32.3 per 100 000adolescents population . Every year 280-290 thousand children and teenagers are infected with Mycobacterium tuberculosis in Russia. The significant increase in cases of adolescent disease are registered from the contact with drug-resistant tuberculosis [4, 5] and, in comparison with children, revealed more severe clinical forms: disseminated, the prevalence of the widespread of infiltrative tuberculosis above the focal with the disintegration of the lung tissue and bacterial secretion [6]. The deaths from drug- resistant tuberculosis are registered in this particular social group risk adolescents because of untimely in identifying.

The deadaptation of adolescent children due to their neuro-psychological imbalances and hormonal changes manifested syndrome of anti-infectious protection with activation opportunistic infections, especially herpes-viral, increasing the risk of infection with Mycobacterium tuberculosis (MBT). The recurrent infection caused by herpes simplex viruses is the most clinically delineated. The secondary immune deficiency is one of the factors in the development of tuberculosis at the beginning of the disease, and then it is the result of the disease [7, 8]. The comprehensive tuberculosis chemotherapy that kills or suppresses the functional activity of the MBT also has a strong immunosuppressive effect. So for prevention of tuberculosis infection and the formation of tolerant for treatment and severe forms of pulmonary tuberculosis in adolescents, the early detection of the adverse triggers factors is necessary.

The comprehensive study of the risk factors of secondary immune deficiency, especially the activation of herpes-viral infections in tuberculosis in adolescents are absent virtually. All of the above taking into account the negative trends in the overall health of adolescent children highlights the need for the development and introduction of modern technology of immunotherapy carried out simultaneously with the causal against tuberculosis chemotherapy, and it was the purpose of the study.

Methods

The prospective clinical and laboratory examination of 62 hospitalized patients was performed in 2008-2011 on the base State Organization of Health “Antituberculosis Clinical Dispensary "Phtisiopulmonology "” the city of Perm for the study of modern clinical and laboratory features of pulmonary tuberculosis in the adolescents, the prevalence and nature of opportunistic herpes-viral infections. The inclusion criteria were age 14-17

years; verified pulmonary tuberculosis, localized form; absence during the 3 months prior to inclusion in the study therapy with recombinant interferon alfa-2b or inducers of endogenous interferon, informed consent of the patient or the patient's parents to participate in the study, the lack of HIV infection. The every teenager with pulmonary tuberculosis surveyed in accordance with the medical and economic standards, tuberculin diagnosis and "Diaskintest" and twice serological screening study (before and 1 month after therapy) regarding the status of specific immunity to HSV, CMV, Epstein-Barr virus (EBV), and interferon status. Using the enzyme immunoassay (EIA) carried out by the conventional method with the test systems Vektor-Best (Novosibirsk city), determined indicators IgG avidity index (AI%) of HSV 1.2 and CMV; IgG to EBV Viral Capsid Antigen (VCA), IFN -α, IFN -γ, antibodies to IFN -α. Specific immune response to infection with HSV , CMV , EBV was estimated based on the amount in the dynamics of IgG titers through 1 month , taking into account clinical and anamnestic data [9 ,10].

The randomized trial of efficacy of interferon -α2-β (VIFERON®) conducted on a "case-control" study with two groups of adolescents with pulmonary tuberculosis isolated from patients studied. The exclusion criteria for interferon therapy of patients of main group(MG) supposed are presence of antibodies to IFN-alpha, which has not been identified. The both studied groups were comparable at diagnosis, blood parameters, level of IgG to HSV, CMV, EBV and interferon status, age, gender and conditions of the basic therapy. The recurrence of HSV infection at the time of initial examination was not observed. The patients of the main group (MG, n = 26) received rectally VIFERON® on the descending scheme: 3 million IU (1 suppository) 1 times a day for 5 days, then 1 million IU (1 suppository) 2 times a day for 5 days, then 1 million IU once a day 2 times a week 10 times. The full cours of treatment last done month with basic comprehensive antituberculous treatment. The patients from comparison group (CG, n = 36) did not received interferon therapy.

The evaluating of the efficiency of immunotherapy in treatment of tuberculosis was undertaken by clinical and X-ray tomography and laboratory criteria, including re-screening ELISA testing for herpes viruses and interferon status after 1 month of interferon therapy and the complete blood count in 1 and 6 months of observation, comparing with the results of the comparison group. Hypothetically, we did not assumed such a significant influence of therapy with VIFERON® for pulmonary tuberculosis as the cavities closed, reduced the time of bacteria excretion and the time of hospitalization. The criteria of efficiency of therapy considered: normalization or a tendency to normalization of separate clinical symptoms of the disease; absolute values of the leucocyte of blood, decreased activity of the infectious process caused by HSV and CMV (no recurrence, reduced titers IgG), increase the level of interferon. The conclusion on the efficiency of interferon therapy was given on the basis of the positive dynamics of indicators inside the group, as well as calculation of the odds ratio.

The statistical processing of the materials was carried out using the software package SPSS for Windows 13,0 and Biostatistics for Windows. The amendment van der Waerden used for calculate the relative values for $n < 30$. Output was considered statistically significant at $p \leq 0,05$.

The main part

The analysis showed that the first place was occupied by chronic diseases of ENT-organs (60.0 %) and recurrent HSV infection (54.8%) in the presence of more than two chronic diseases in 75.8% in-patient adolescents with newly diagnosed pulmonary tuberculosis averaged markers secondary immune deficiency. In the majority of cases (98.4%) different deviations of the parameters of peripheral blood were decrease in the number of lymphocytes (53,2%)that corresponded to the most significant indicators of clinical markers. The changes in serum detected in 96.8% of cases, mainly in the form of dysproteinemia by increasing the globulin fraction (88.7%).The activity of inflammatory changes was also confirmed by an increase in C-reactive protein at 29.0% and fibrinogen levels - in 27.4% of patients. As a result primary screening study of blood serum by enzyme immunoassay (EIA) was found that seropositive for HSV 1,2 were - 91,9 ± 3,7%, CMV - 95,2 ± 2,7% and EBV - 100% of the patients. High titers of IgG antibodies to HSV were registered in 90,3 ± 4,1% of cases, CMV - in 93,6 ± 3,2% (at high values of avidity index and the absence of acute clinical picture). This intensity of antibody production indicates on serological activation of chronic infectious process. Depending on the level of antibody against HSV and CMV on the form and extensiveness of tuberculosis process in the lungs is not received, as well as IgG titers to HSV and CMV were as high (more than 1:2000) in the majority of patients with pulmonary tissue destruction. The low level IgG antibodies to EBV VCA (100%) testified to anamnestic immunity. With regard to interferon status, the level of IFN-alpha were low in most cases, there were zero or below normal in 29.0% of patients, the proportion of IFN-gamma indicators "below the norm" was 48.4%, zero - 29, 0%, indicating that the

virtual absence of lymphocytic production "late" interferon in 77.4% of in-patients on a background of mixed viral and bacterial infections, and not contradict the data of other researchers [11]. Antibodies to IFN-a has not been identified.

All of the above was the reason for the development of immunotherapy in the combined treatment of adolescents with pulmonary tuberculosis. The choice of drug interferon-α2-β (VIFERON ®) was due to its multifunctionality therapeutic effects: substitution, immunomodulation, antiviral and antioxidant activity with a well-studied efficacy in the combined treatment of various diseases, including herpes virus infection. This medicine is not invasive; rectal administration reduces the burden on the hepatic blood flow during rapid absorption. It is produced in the form of suppositories, including in high doses 1,000,000 and 3,000,000 IU applicable to adolescents with viral-bacterial mixed infections. VIFERON ® is well tolerated, compatible with all drugs, convenient and economically available for mass use in the hospital. Clinical studies of VIFERON® efficacy in the combined treatment of pulmonary tuberculosis in adolescents are rare [12]. Integrated clinical and laboratory studies have not been conducted.

Dynamics of clinical and laboratory criteria was as follows: the reduction in arrhythmia frequency was achieved to 15.4% in MG against 44.4% in CG after1 month of interferon therapy (p = 0,033); increase in body weight in 84.6 % of adolescents, on average at 3,83 ± 0,65 kg in MG against CG - to 1,5 ± 0,41 kg (p = 0,04); increase in absolute lymphocyte count by 46.1 %in MG against the CG - to 11.2 % (p = 0.005); decreased serological activation in relation to HSV - 30.8 % in MG against CG - in 8,3% (p = 0,051);in relation to CMV - 61.5 % in MG against CG - in 30,6% (p = 0,031); increasing the amount of interferon -alpha - 61.5 % in MG against CG - 22,2% (p = 0,004) and interferon - gamma - 61.5 % in MG against CG - in 30,6% (p = 0,031).

Very important result of testifying prolonging effect interferon therapy was a significant increase in the percentage (up to 44,6 ± 1,72% in the MG against 37,05 ± 1,4% in CS, p = 0,006) and the average of the absolute number of lymphocytes (up to 2773 5 ± 117,0 10^6/ l in the MG against 2380,6 ± 104,0 10^6 / l in CG, p = 0,047) in patients of the MG by the end of in-patient therapy (6 months) for the achievement of all individual normative absolute indicators, while in the CG low level of lymphocytes remained at 22.2%.

The recurrence of HSV was not observed during treatment for one month in both groups. Recurrences of chronic HSV in localized skin form occurred after 1 month in MG 1 out of 15 against in CG 3 out of 20, and later still in 4 teenagers in the CG. Recurrence rate: in MG is 1/15 (6.7%) against in CG - 7/20 (35 %). The recurrences were absent for all five months after interferon therapy. The value odds ratios calculated (OR = (14/1) / (13/7)) to assess the association between measures of therapeutic effect on HSV infection and clinical course (effect on/off) that showed how much the probability of a positive therapeutic effect in main group than in the comparison group.

The chance of positive dynamics course of chronic recurrent HSV on the background interferon therapy in the main group was 7.5 times higher (p = 0.05).

During the safety assessment interferon therapy using "information sheet" in MG patients were registered 7 undesirable actions (26.9%, 7/26) against in CG - 29 (80,6%) (p = 0,000) on the background of the basic chemotherapy of pulmonary tuberculosis in adolescents at the period of the first month of in-patient treatment. All undesirable actions were associated with antituberculous chemotherapy. Immunotherapy with VIFERON® at this time was not canceled. Exacerbations of cutaneous allergy was not observed in the main group, even in adolescents with of aggravated allergic history, while in CG four patients noted the appearance of mild allergic rash with mild pruritus in patients receiving Pyrazinamide.

Findings

Proven efficacy and safety of schedule treatment with VIFERON® on the background of the basic chemotherapy of pulmonary tuberculosis in adolescents and significant impact on the reduction of side effects traditionally prescribed medications allow to consider this method is a scientifically sound and appropriate.

Conclusions

1. Recurrent opportunistic infection caused by the herpes simplex virus, detected in 54.8% adolescents with pulmonary tuberculosis in the presence of high titers of IgG antibodies to HSV (90.3%) and CMV (93.6%).

2. Indicators of widespread secondary immune deficiency are decrease in absolute lymphocyte count (54.8%), violation of products of immunoglobulin (88.7%) and of interferon (IFN-alpha - 29%, IFN-gamma - 77.4%).

3. Inclusion of antiviral and immunomodulation drug VIFERON ® in combined treatment of pulmonary tuberculosis in adolescents with recurrent HSV infection leads to significant reduction of IgG antibodies to HSV (30.8%) and CMV (61.5 %) with a probability of positive clinical dynamics 7.5 times higher than in the comparison

group (p = 0.05). Indicators of clinical and laboratory efficacy of immunotherapy are reducing the frequency of arrhythmias and increase in body weight, increasing the number of lymphocytes and interferon-alpha and gamma. At the same time 3-fold reduced incidence of side effects of a specific chemotherapy.

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