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IMMUNOLOGICAL ASPECTS OF VACCINATION IN HIV-INFECTED PATIENTS

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Abstract. Until recently, HIV infection does not lose its relevance. In 2022, 630 000 people died and 1.3 million people became infected with the human immunodeficiency virus (HIV). HIV-positive persons develop more infectious diseases than healthy people do; the causative agents are mainly opportunistic microorganisms. *Streptococcus pneumoniae* is the main causative agent of infection in the lungs in HIV-infected persons. In order to prevent the development of severe pneumococcal infections and to overcome antibiotic resistance, vaccines have been developed. There are polysaccharide (PPV) and conjugate (PCV) vaccines. According to clinical recommendations, vaccination of previously unvaccinated HIV-infected patients is carried out regardless of T-helper cell level. However, no data were found on the effect of PCV13 on immunological memory cells. The purpose of this study is to assess an effect of PCV13 vaccination on the immune system in HIV-infected subjects. *Materials and methods.* The study included 200 patients with HIV infection, which were divided into two groups: I — received a dose of PCV13 (n = 100) and control group (n = 100). During the first visit, immunological and microbiological studies were carried out. On the second visit, a PCV13 was injected into the deltoid muscle. The third visit was made a year later, where immunological and microbiological studies were repeated. Participants were divided into 4 subgroups depending on $CD4^+$ T cell level. The microbial study was done using a swab collected from the back of the throat. *Results.* During the immunological examination at visit 1, abnormalities were detected in all examined populations and immune cell subsets. At 12 months post-vaccination, the median levels of $CD3^+CD4^+$ and $CD45^{RO+}$ T lymphocytes in the immunized group were higher than pre-vaccination levels compared to control group, in which the values changed insignificantly. Our data confirm the immunological effectiveness of PCV13 administration in HIV-infected patients. In patients with peripheral blood $CD19^+$ lymphocyte deficiency, had increased microbial detection rate (p = 0.003). *Conclusion*. As a result, due to the high risk of pneumococcal pneumonia, HIV-infected patients should be immunized with a 13-valent pneumococcal conjugate vaccine.

Key words: *HIV-infected, PCV13, Streptococcus pneumoniae, vaccination, pneumococcal pneumonia.*

ИММУНОЛОГИЧЕСКИЕ АСПЕКТЫ ВАКЦИНАЦИИ ВИЧ-ИНФИЦИРОВАННЫХ ПАЦИЕНТОВ

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Резюме. Проблема ВИЧ-инфекции не теряет своей актуальности до настоящего времени. В 2022 г. 630 000 человек умерли и 1,3 млн человек заразились вирусом иммунодефицита человека (ВИЧ). У ВИЧ-инфицированных, в отличие от здоровых лиц, чаще развиваются инфекционные заболевания, возбудителями которых являются в основном условно-патогенные микроорганизмы. Основным возбудителем пневмонии у ВИЧ-инфицированных является *Streptococcus pneumoniae*. Для предотвращения развития тяжелых форм

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пневмококковой пневмонии и преодоления антибиотикорезистентности разработаны вакцины, содержащие антигены из капсулы *S. pneumoniae*. Созданы и активно применяются в клинической практике пневмококковые полисахаридные (ППВ) и пневмококковые конъюгированные вакцины (ПКВ). Однако не обнаружено данных о влиянии ПКВ13 на клетки иммунологической памяти. Целью данного исследования является изучение влияния вакцинации ПКВ13 на иммунную систему у ВИЧ-инфицированных лиц. *Материалы и методы.* В исследование были включены 200 больных ВИЧ-инфекцией, которые были разделены на две группы: I, получившая дозу ПКВ13 (n = 100), и контрольная (n = 100). Во время первого визита были проведены иммунологические и микробиологические исследования. Во второй визит осуществлялось введение в дельтовидную мышцу ПКВ13. Третий визит был выполнен через 1 год, повторно проводились иммунологическое и микробиологическое исследования. Участники были разделены на 4 подгруппы в зависимости от уровня $CD4^+$ клеток. Микробиологическое исследование проводилось в материале мазка с задней стенки глотки. *Результаты.* При проведении иммунологического обследования на визите 1 были выявлены отклонения во всех изученных популяциях и субпопуляциях клеток иммунной системы. Через 12 месяцев после вакцинации медиана уровня $CD3^+CD4^+$ и $CD45^{RO+}$ лимфоцитов в иммунизированной группе стала выше довакцинального уровня, в отличие от контрольной группы, в которой значения статистически не изменились. Наши данные подтверждают иммунологическую эффективность введения ПКВ13 у ВИЧ-инфицированных пациентов. У больных с дефицитом $CD19^+$ лимфоцитов в периферической крови выявлено увеличение частоты выделения микроорганизма (p = 0,003). *Заключение.* Таким образом, в связи с высоким риском развития пневмококковой пневмонии ВИЧ-инфицированные больные должны быть вакцинированы 13-валентной пневмококковой конъюгированной вакциной.

Ключевые слова: *ВИЧ-инфекция, ПКВ13, Streptococcus pneumoniae, вакцинация, пневмококковая пневмония.*

Introduction

In 2022, 630 000 people died and 1.3 million people became infected with the human immunodeficiency virus (HIV), and there are 39 million people living with HIV (PLHIV) in the world [14]. In the Russian Federation in 2022, 63 150 new cases of infection were detected, 34 410 people died, which is 0.9% more than in 2021 [6].

The causative agents of infectious diseases in PLHIV are opportunistic microorganisms [11]. In 25–60% of HIV-infected patients, lung damage of infectious origin (tuberculosis, pneumocystis and bacterial pneumonia) is observed [3]. The most common causative agents of community-acquired pneumonia are *S. pneumoniae* (up to 20%), *H. influenzae* (10–15%) and *S. aureus* (5–10%). Pneumonia caused by *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* also occurs, but is quite rare [1, 2, 4, 5, 7, 9].

To prevent the development of severe forms of pneumococcal infections and to overcome antibiotic resistance, vaccines have been created. Polysaccharide (PPV) and conjugated (PCV) pneumococcal vaccines have been developed. The 13-valent conjugate pneumococcal vaccine contains antigens from thirteen serotypes of pneumococcus, and the 23-valent polysaccharide vaccine contains from twenty-three serotypes [7]. PCV13 contains polysaccharide antigens conjugated to a carrier protein (diphtheria toxoid CRM197). This binding of molecules allows one to attract T-lymphocytes to the site of inflammation and increase the effectiveness of the immune response. PCV13 is approved for use in children from 6 months of age; it reduces the carriage of pneumococcus on the mucous membrane of the upper respiratory tract and does not require repeated administration in adults.

According to clinical recommendations, vaccination of HIV-infected against pneumococcus, who have not been previously vaccinated, is carried out regardless of the level of T-helpers. Previously unvaccinated people are given PCV13, no earlier than 8 weeks later PPV23 is given, after 5 years PPV23 is revaccinated [8].

Several studies have been conducted to evaluate the effectiveness of PCV13 in HIV-infected adults. Research carried out at the University Hospital of Reims to determine the immunological efficacy of PCV13 in PLHIV. As a result was found that a single vaccination leads to a positive immunological response and protection 1 month after vaccination in a group of patients with an initial $CD4^+$ level of 200 cells/μl and a $CD4^+/CD8^+$ ratio more than 0.8. After 6 and 12 months, the percentage of protected patients decreases. In addition, after vaccination with PCV13, an increase in the opsonophagocytic reaction of anti-pneumococcal antibodies was noted [12].

A study from South Korea examined the effectiveness of PCV13 in PLHIV depending on baseline T-helper cell levels [13]. A lower immune response to the vaccine was found in individuals with a T-helper cell count of less than 350 cells/μL. In addition, lower levels of specific IgG were reported in this group.

A meta-analysis that included 28 cohort studies and 11 randomized clinical trials examined the effectiveness of different pneumococcal vaccination regimens [10]. The immunological effectiveness of PCV13 administration has been demonstrated. At the same time, multiple vaccination led to only a slight increase in IgG and was not economically effective.

Limitations of the different studies include the absence of information about the effect of PCV13 administration on immunological memory cells. In addition, the main attention was paid to the assessment of the T-cell component of immunity and the effect on B cells was not presented. However, it is B-lymphocytes produce antibodies, which are a key link in the fight against pneumococcus.

The purpose of the study is to evaluate the immunological efficacy of PCV13 vaccination in HIV-infected people.

Materials and methods

In the study were included 200 HIV-infected people, which were divided into two groups: I — received a dose of PCV13 (n = 100) and control (n = 100).

For the entire period of the study, for patients were planned 3 visits. At the first visit, the following studies were performed: microbiological examination of a smear from the posterior pharyngeal wall, immunological examination of peripheral blood (determination of $CD3^+CD4^+$, $CD19^+$, $CD45^{RO+}$ lymphocytes). The second visit was only for the immunized group, where PCV13 was injected into the deltoid muscle. The third visit was performed after 12 months, immunological and microbiological studies were repeated.

Determination of populations and subpopulations of lymphocytes was carried out by flow cytometry. Depending on the level of $CD4^+$ cells (T-helpers), the participants were divided into 4 subgroups: 1st — from 50 to 199 cells/μl of blood (immunized group n = 19, control group n = 25); 2nd — 200–349 cells/μl (immunized group n = 20, control group n = 14); 3rd — 350–499 cells/μl (immunized group n = 17, control group n = 21); 4th — 500 or more cells/μl. (immunized group n = 44, control group n = 40).

To conduct a microbiological study, a smear was taken from the posterior pharyngeal wall. The biomaterial was seeded on the following media: media: 5% blood agar, chocolate agar, Sabouraud's medium, universal chromogenic media. The isolated strains were identified by matrix-activated laser desorption/ionization time-of-flight (MALDI-ToF) mass spectrometry.

Statistical data processing was carried out using the Statistica 13.0 program (STATSOFT, USA; license 2883). All the studied samples were distributed abnormally, so non-parametric statistics methods were applied to their study. The results were considered statistically significant if the significance level (p) was less than 0.05.

Results and discussion

At the first visit, the following median lymphocyte levels were obtained in vaccinated patients (Fig. 1). The median level of T-helpers in those examined in the 1st subgroup was 115 cells/μl, in the 2nd subgroup — 254.5 cells/μl, in the 3rd subgroup — 421 cells/μl, in the 4th subgroup — 663.5 cells/μl. At the 3rd visit, there was an increase in the 1st subgroup up to 205 cells/μl (p = 0.001), in the 2nd one — up to 377 cells/μl (p = 0.001), in the 3rd one — up to 478 cells/μl (p = 0.004) and in the 4th — up to 735 cells/μl (p = 0.096).

The dynamics of changes in the number of B-lymphocytes in all the studied subgroups had no statistical significance. At the same time, a statistically significant increase in the number of cells involved in the mechanisms of immunological memory ($CD45^{RO+}$ lymphocytes) was registered in vaccinated PLHIV. The value of the median level of $CD45^{RO+}$

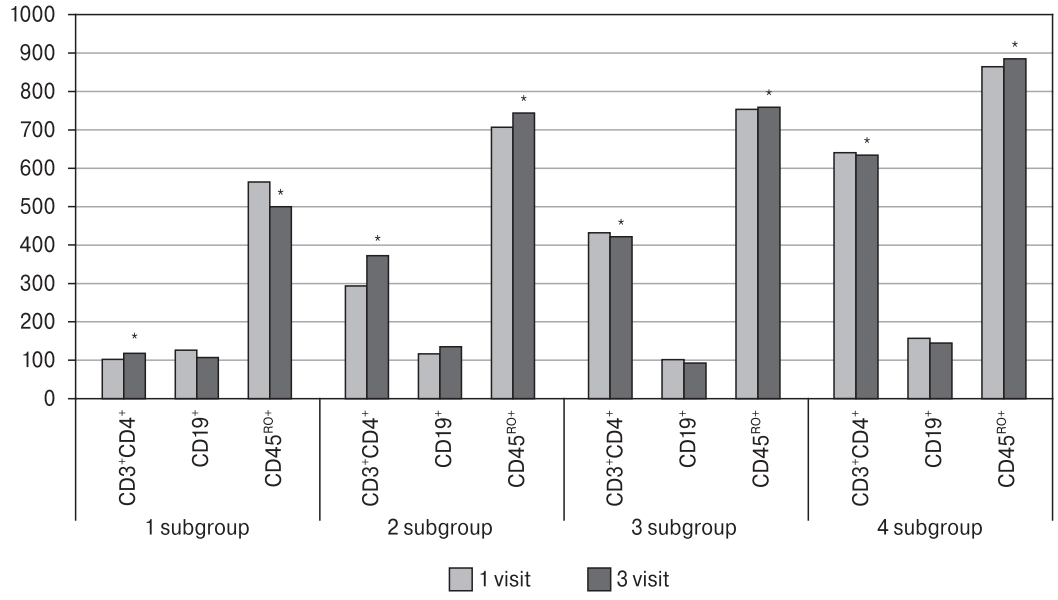

Figure 1. The value of the median parameters of the immunogram in patients of the immunized group at visits 1 and 3
Note. *p < 0.05.

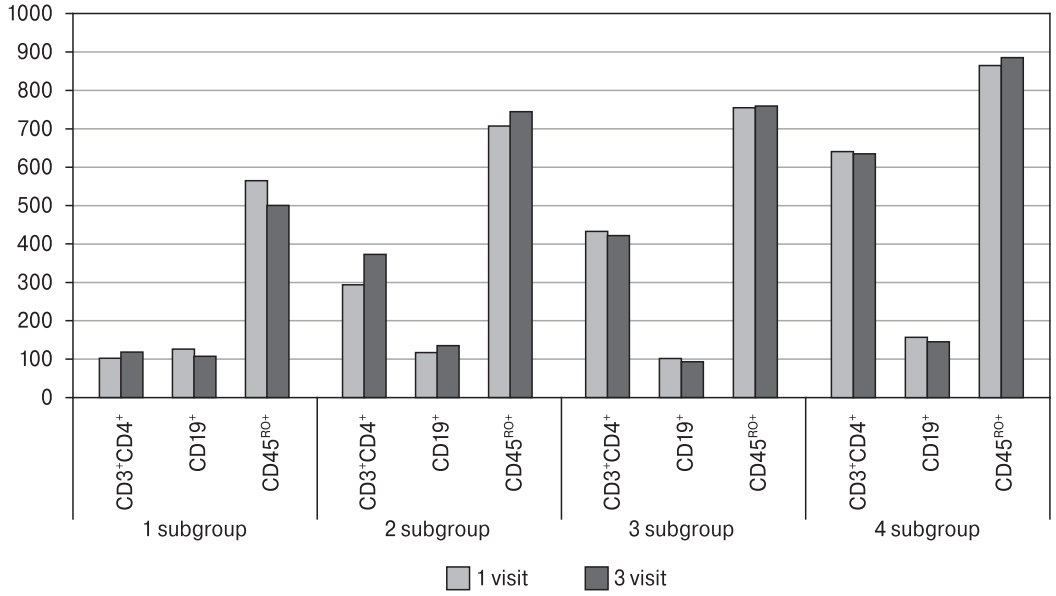

Figure 2. The value of the median of immunogram parameters in patients of the control group at visits 1 and 3

lymphocytes in the first subgroup increased from 556 cells/μl at visit 1 to 623 cells/μl at visit 3 (p = 0.030); in the second subgroup from 778.5 cells/μl to 818 cells/μl (p = 0.028); in the third subgroup from 701 cells/μl to 749 cells/μl (p = 0.022); in the fourth subgroup, from 848 cells/μl at the 1st visit to 924 cells/μl at the 3rd visit (p = 0.01).

Participants in the control group showed no statistically significant changes in the median levels of $CD3^+CD4^+$, $CD19^+$, $CD45^{RO+}$ lymphocytes in all four subgroups (Fig. 2). The dynamics of changes in the content of T-helpers in peripheral blood was: in the examined in the 1st subgroup — from 102 cells/μl to 118 cells/μl (p = 0.322), in the 2nd — from 293.5 cells/μl to 372.5 cells/μl (p = 0.164), in the 3rd subgroup — from 432 cells/μl to 421.5 (p = 0.446), in the 4th subgroup from 640 cells/μl to 634 cells/μl (p = 0.326).

A similar trend was found when assessing the median of B cells: in the first subgroup from 126 cells/μl to 107 cells/μl (p = 0.717), in the second subgroup — from 117 cells/μl to 135 cells/μl (p = 0.808). In addition, there were no statistically significant differences in the change in the level of median immunological memory cells. In the 1st subgroup, their value decreased from 564 to 499.5 cells/μl (p = 0.478), in the 2nd, 3rd and 4th subgroups it increased from 706.5 to 743.5 cells/μl (p = 0.520), from 640 to 758.5 cells/μl (p = 0.542), from 864 to 884.5 cells/μl (p = 0.412), respectively.

When conducting a statistical analysis, a correlation was found between the level of B-cells in the peripheral blood and the detection of pneumococcus on the mucous membrane of the upper respiratory tract. In those examined with a deficiency of $CD19^+$ lymphocytes in the peripheral blood, an increase in the frequency of isolation of the microorganism was found (p = 0.003).

Thus, the obtained data correlate with literary sources and confirm the immunological effectiveness of PCV13 administration [10, 12, 13]. A pronounced stimulation of the cellular link of the immune system was revealed, which was expressed in a statistically significant increase in the level of T-helpers in those examined with a $CD3^+CD4^+$ deficiency at the time of the start of the study. It is important to note that immunization led to an increase in the number of immunological memory cells, which demonstrates the effectiveness of the vaccination. At the same time no statistically significant differences were found in the control group.

Conclusion

Thus, the introduction of a 13-valent pneumococcal conjugate vaccine to HIV-infected patients causes immunological effects and can effectively reduce the risk of infections caused by *S. pneumoniae*.

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