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ФАГОТЕРАПИЯ АНТИБИОТИКОРЕЗИСТЕНТНОЙ ПНЕВМОНИИ: ИММУНОМОДУЛЯЦИЯ ИЛИ ПЕРЕРАСПРЕДЕЛЕНИЕ?

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Резюме. Наше сообщение касается наблюдений, сделанных в ходе лечения пневмонии индивидуально подобранными бактериофагами у больных с ИСМП, находящихся на ИВЛ.

Обследовано 19 пациентов, находящихся на ИВЛ, состояние которых осложнилось антибиотикоустойчивой пневмонией.

Лечение больных было дополнено фаготерапией, бактериофаги были подобраны индивидуально для каждого больного с учетом микробной этиологии заболевания (*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*).

Иммунофенотипирование лимфоцитов крови проведено с помощью 2-3-параметровой проточной цитометрии. Функциональная активность лейкоцитов крови оценивалась по их способности продуцировать при культивировании IFNα и IFNγ. Уровень продукции интерферонов в собранных после культивирования супернатантах количественно оценивался как по их концентрации (метод ИФА, реагенты ЗАО «Вектор-Бест-Европа»), так и по их биологической активности.

Статистическая обработка результатов проведена с использованием программы Statistica 6 по непараметрическому U-критерию Манна–Уитни.

В ходе успешной фаготерапии пневмонии индивидуально подобранными бактериофагами в крови пациентов отмечается преодоление лимфопении (в случаях, если она была) и увеличение как количества, так и функциональной активности лимфоцитов периферической крови у всех больных.

Зависимость между микробной нагрузкой (моно- или микст-инфекция, количество КОЕ возбудителей пневмонии, потребность в повторных курсах фаготерапии) и степенью дефицита в тех или иных субпопуляциях лимфоцитов не была выявлена.

Достигнутая после одного курса фаготерапии активация иммунной системы сохранялась по крайней мере в течение 3 недель после прекращения введения фагов.

Ключевые слова: фаготерапия, влияние на иммунную систему, активированные Т-лимфоциты, NK-клетки, IFNγ, IFNα, антибиотикорезистентная пневмония

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PHAGE THERAPY IN ANTIBIOTIC RESISTANT PNEUMONIA: IMMUNOMODULATION OR REDISTRIBUTION?

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Abstract. Our report concerns the observations made during the treatment of pneumonia with individually selected bacteriophages in HCAI patients on mechanical ventilation.

19 patients on mechanical ventilation whose condition was complicated by antibiotic-resistant pneumonia were examined.

The treatment of patients was supplemented with phage therapy, bacteriophages were selected individually for each patient, taking into account the microbial etiology of the disease (*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*).

Immunophenotyping of blood lymphocytes was carried out using 2-3-parameter flow cytometry. The functional activity of blood leukocytes was assessed by their ability to produce IFNα and IFNγ during cultivation. The level of interferons production in supernatants collected after cultivation was quantitatively evaluated both by their concentration (ELISA, reagents from "Vector-Best-Europe", Russia) and by their biological activity.

Statistical processing of the results was carried out using the Statistica 6 program according to the nonparametric Mann-Whitney U-test.

In the course of successful phage therapy with individually selected bacteriophages overcoming of lymphopenia (if there was one) and an increase in both the number and functional activity of peripheral blood lymphocytes in all patients with pneumonia observed are noted.

The relationship between the microbial load (mono- or mixed infection, the number of CFU pathogens of pneumonia, the need for repeated courses of phage therapy) and the degree of deficiency in one or another subpopulation of lymphocytes was not detected.

Activation of the immune system achieved after one course of phage therapy was maintained for at least 3 weeks after phage administration was discontinued.

Keywords: phage therapy, effects on the immune system, activated T lymphocytes, NK cells, IFNγ, IFNα, antibiotic-resistant pneumonia

Introduction

The development of pneumonia as a complication caused by health care associated infections (HCAI) (the earlier term is "nosocomial infections") in patients who have been on artificial lung ventilation (ALV) for a long time (mechanical ventilation) is a significant problem, especially in cases of antibiotic resistance of pathogenic microflora.

The list of HCAI pathogens includes representatives of various taxonomic groups of bacteria, viruses, protozoa and fungi. More than 90% of all nosocomial infections are of bacterial origin and, moreover, HCAI are usually caused by hospital strains of microorganisms. The incidence rate of HCAI in resuscitation departments and intensive care units is 5-10 times higher than in patients of other departments. HCAI pathogens are mostly antibiotic resistant and frequently there are multidrug resistant microorganisms [1, 14]. ALV-associated pneumonia develops in 5% of intensive care unit patients.

The use of bacteriophages is a modern approach to the treatment of these types of complications caused by HCAI. [2]. In addition to the known specific lytic effect of phages against the corresponding target bacteria, there is literature evidence of other effects of phages in the human body, the immunomodulating effect in particular [5, 9, 10]. At the same time, the effect of phage therapy on the immune system is not well studied.

Our report concerns the observations made during the treatment of pneumonia with individually selected bacteriophages in HCAI patients on mechanical ventilation.

Materials and methods

We examined 19 patients on mechanical ventilation whose condition was complicated by antibiotic-resistant pneumonia.

The treatment of patients was supplemented with phage therapy, bacteriophages were selected individually for each patient, taking into account the microbial etiology of the disease (*Pseudomonas aeruginosa*,

Klebsiella pneumoniae, *Acinetobacter baumanii*) in full accordance with the algorithm protected by the Russian Federation patent for an invention [13].

Phage therapy course duration was 5 days. In some cases, it took more than one course of phage therapy and/or the use of bacteriophages cocktail.

The patient's immune system state was assessed before the start of phage therapy and weekly after it began (a total of 2-5 times).

Immunophenotyping of blood lymphocytes was carried out using 2-3-parameter flow cytometry (reagents and equipment from "Beckman Coulter", USA). Serum concentration of IgG, IgA, IgM was determined by turbidimetry (reagents from "Human", Germany). The functional activity of blood leukocytes was assessed by their ability to produce IFNα and IFNγ during cultivation (stimulants are Newcastle disease virus and PHA, respectively; doses and stimulation regimen were used in accordance with [6]). The level of interferons production in supernatants collected after cultivation was quantitatively evaluated both by their concentration (ELISA, reagents from "Vector-Best-Europe", Russia) and by their biological activity, in accordance with [6]. The biological activity of interferons was expressed in U/ml which corresponded to the 1/titer of the abolition of the cytopathic effect of the virus on the human embryo lung fibroblasts after their incubation with supernatants of stimulated blood cell culture. Statistical processing of the results was carried out using the Statistica 6 program according to the nonparametric Mann–Whitney U-test.

Results and discussion

Before the start of phage therapy, half of the examined patients showed lymphopenia, a reduced number of cytolytic T lymphocytes (CTL), and NK cells. A decrease in the number of CTL in most patients was combined with an increase in the percentage of activated cells among them ($CD3^+CD8^+CD38^+$). A decrease in the number of T helpers in the blood was detected in 68.4% of patients, but no increase in the number of activated ones was detected among them.

In comparison with the normal level, B lymphocyte deficiency was registered in less than half of the patients, and a decrease in IgG concentration was detected in the blood serum of 5 people (26.3%).

The decrease in the number of T helpers and CTL was accompanied by a decrease in their ability to produce IFNγ, which was discovered both by the concentration of IFNγ in the culture supernatants and by the biological activity of these supernatants, while the production of IFNα practically did not decrease.

The average values of these parameters, as well as their change immediately after the course of phage therapy are shown in the Table 1.

In Table 1 you can see that at the end of the one course of phage therapy, the average numbers and functional activity of lymphocytes increase, but most of the changes are not statistically significant. The reason for this is the probable effect on the immune system state of patients not only of pneumonia itself, but of factors associated with the underlying disease of the patients, which was the reason for their hospitalization.

There was also some heterogeneity of patients according to the nature of the response to phage therapy. Thus, in 9 people out of 19, airway sanitation was achieved after 1 course of treatment with one bacteriophage strain (group 1). However, the other 10 patients required 2-3 courses or a combination of several phages and some patients, in addition to the respiratory tract, required sanitation for another 1-2 infection loci (group 2).

The state of the immune system in both groups was similar: the proportion of patients with lymphopenia and cell deficiency in individual subpopulations of lymphocytes was almost the same. However, some features can be noted.

The percentage of activated T cells $CD3^+CD8^+CD38^+$ was increased initially in patients of both groups, and the proportion of $CD3^+$HLA-DR^+ in group 2 was slightly lower than in group 1 (6.9 *versus* 10.9%), and after one course of phage therapy its increase was significant (15.0%, $p = 0.023$).

The initial level of IFNγ production in group 2 was also lower than in group 1 (1849 *versus* 4130 pg/ml), and after one course of phage therapy it increased significantly (7688 pg/ml, $p = 0.047$), whereas in group 1 the ability of leukocytes to produce IFNγ increased to a lesser extent (from 4130 to 5253 pg/ml).

To statistically evaluate the results obtained and at the same time take into account interindividual variability, the change in each parameter was analyzed by us not only in units of laboratory analysis, but also as a percentage of the initial state.

Table 2 in this aspect presents the dynamics of individual indicators for a period of 3 weeks after the start of phage therapy. From 19 patients, 11 were observed by us for 3 or more weeks, including 5 people from group 1 and 6 people from group 2.

Table 2 demonstrates that immediately after the completion of one course of phage therapy, the number of lymphocytes in such subpopulations as T helpers and NK cells significantly increases. Considering whether there was a deficiency of these cells in each patient before the start of phage therapy and its level, the magnification rate was different, but on average it was 1.5 for T helpers and 1.5-2 times for NK cells.

Functional activity of lymphocytes was also registered at a higher level. The percentage of $CD3^+$HLA-DR^+ increased immediately after 1 course of phage therapy and remained at this and higher level for 3 weeks of observation. The percentage of $CD3^+CD8^+CD38^+$ increased to a lesser extent, but this parameter was already initially increased in patients compared to parameters of healthy people (see Table 1).

The ability of blood lymphocytes to produce IFNγ also increased after phage therapy and continued to

TABLE 1. CHANGE IN THE IMMUNE SYSTEM STATE OF PATIENTS AT THE END OF ONE COURSE OF PHAGE THERAPY

		Before phage therapy	After 5-10 days	Normal limits
Lymphocytes (10^3/ml)		1407	1698	1500-2800
T cells ($CD3^+$, 10^3/ml)		1075	1276	1100-2000
T helpers ($CD3^+CD4^+$, 10^3/ml)		673	762	750-1200
CTL ($CD3^+CD8^+$, 10^3/ml)		370	470	300-700
$CD4^+/CD8^+$		2.12	1.83	1.6-3.00
B cells ($CD3^-CD19^+$, 10^3/ml)		138	159	100-500
NK cells ($CD3^-CD16^+CD56^+$, 10^3/ml)		161	227	150-550
Activated T cells	$CD3^+CD69^+$ (%)	3.2	3.3	< 10
	$CD3^+HLA\text{-}DR^+$ (%)	8.7	15.5* p = 0.03	< 10
	$CD3^+CD8^+CD38^+$ (%)	15.9	27.1* p = 0.04	< 10
Concentration in serum	IgG, mg/ml	9.3	–	7.6-18.9
	IgM, mg/ml	1.2	–	0.5-3.4
	IgA, mg/ml	2.4	–	0,8-3.5
IFNγ production	concentration, pg/ml	2990	6785* p = 0.04	2000-25000
	biol. activity, U/ml	15	24	32-128
IFNα production	concentration, pg/ml	231	260	100-500
	biol. activity, U/ml	110	130	160-640

Note. *, significant difference from the level before phage therapy.

TABLE 2. DYNAMICS OF THE IMMUNE SYSTEM STATE OF PATIENTS WITHIN 3 WEEKS AFTER PHAGE THERAPY

Indicator	Average value of changes in % of the initial state		
	just after	in 2 weeks	in 3 weeks
NK cells ($CD3^-CD16^+CD56^+$)	188 p = 0.01	206 p = 0.02	135
T helpers ($CD3^+CD4^+$)	149 p = 0.03	142	126 p = 0.01
Activated T cells ($CD3^+HLA\text{-}DR$)	157 p = 0.04	227 p = 0.01	211 p = 0.03
Activated T cells ($CD3^+CD8^+CD38^+$)	110	120	180
IFNγ (biol. activity)	173	246 p = 0.04	180 p = 0.03
IFNα (biol. activity)	108 p = 0.03	107	98

Note. As for Table 1.

increase or remained at the achieved level throughout the observation period, and the change in IFNα production did not occur in all patients and was not statistically significant.

Although the stimulating effect of bacteriophages on the immune system, shown in experiments *in vivo* and *in vitro* is known from the literature [4, 8, 10, 15], the changes that we observed in the immune status of patients after phage therapy would probably be more correctly regarded as not immunostimulation, but redistribution of lymphocytes between individual sites of the immune system.

It is believed that immune protection in the lungs is provided by both non-recirculating cells of innate immunity [3] and T cells. The role of memory T cells is to rapidly deploy a specific immune response, acti-

vate the resident elements of the immune system, and attract circulating immune cells to the lungs [7]. It was shown that the outcome of a pulmonary infection associated with *Pseudomonas aeruginosa* depends on the number of T helpers and the polarization of the immune response at their level [12], and NK cells are the main producers of IFNγ in the lungs and are rapidly activated for this purpose (within 1 day [11]).

It is possible that the decrease in antigenic load in the respiratory tract, achieved immediately with successful phage therapy, reduces the need for these cellular elements, and an additional number of lymphocytes, including activated ones, appear in the peripheral blood. The question of whether the state of the immune system after 3 weeks or more is associated with the immunomodulating effect of the bacteriophage remains open.

Conclusion

Thus, in the course of successful phage therapy with individually selected bacteriophages overcoming of lymphopenia (if there was one) and an increase in both the number and functional activity of peripheral blood lymphocytes in all patients with pneumonia.

The relationship between the microbial load (mono- or mixed infection, the number of CFU pathogens of pneumonia, the need for repeated courses of phage therapy) and the degree of deficiency in one or another subpopulation of lymphocytes was not detected.

Activation of the immune system achieved after one course of phage therapy was maintained for at least 3 weeks after phage administration was discontinued.

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