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CLINICAL-IMMUNOLOGICAL EFFECTIVENESS OF RIBOMUNYL IN CHILDREN WITH VIRUS-INDUCED BRONCHIAL ASTHMA

E.B. Belan, E.M. Nikiforova, T.E. Zayachnikova, I.N. Shishimorov, O.V. Magnitskaya

Volgograd State Medical University
1, Pavshikh Bortsov Sq., Volgograd, Russia, 400131

E-mail: belan.eleonora@yandex.ru

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The aim of the study is to research the effects of immunostimulant Ribomunyl in virus-induced bronchial asthma (VBA) children.

Materials and methods. 14 virus-induced bronchial asthma (VBA) children were agministrated with immunostimulant Ribomunyl as a part of complex therapy in a 18-month trial (3 cycles of treatment). The comparison group consisted of 16 patients who received only standard therapy for bronchial asthma. At the end of the study, against the background of basic BA therapy, the following parameters were estimated: the frequency of acute respiratory viral infections (ARVI), the need for antibacterial therapy, the frequency of IgG to respiratory-syncytial virus (RSV) prevalence, the serum level dynamics of total IgE, IFN-γ, interleukin-4 (IL-4), interferon gamma (IFN-γ).

Results. The inclusion of Ribomunyl into the basic therapy complex in virus-induced bronchial asthma (VBA) children, made it possible to reduce the need for the VBA basic therapy complex by 50% and by 12,5% (p=0,0279). At the same time, as for the frequency of acute respiratory viral infections (ARVI), there was a comparable decrease in both groups, but in the main group the number of cases requiring antibiotic therapy decreased from 78.6% to 42.9% (p=0.0199). The inclusion of Ribomunyl into the basic therapy complex resulted in the decrease of the total IgE serum level; in the patients with the initial presence of IgG to the respiratory syncytial virus (RSV), the IL-4 level decreased and the IFN-γ level increased.

Conclusion. Ribomunyl improves the treatment of virus-induced bronchial asthma (VBA) children, herewith the dynamics of immunological indicators is more in RSV-seropositive patients.

Keywords: bronchial asthma, children, Ribomunyl, virus-induced bronchial asthma

Abbreviations: VBA – virus-induced bronchial asthma; ICS – inhaled corticosteroids; INF – interferon; IL – interleukin; ARVI – acute respiratory viral infection; RSV – respiratory syncytial virus; Ig – immunoglobulin; TLR – Toll-like receptors.

КЛИНИКО-ИММУНОЛОГИЧЕСКАЯ ЭФФЕКТИВНОСТЬ РИБОМУНИЛА У ДЕТЕЙ С ВИРУС-ИНДУЦИРОВАННОЙ БРОНХИАЛЬНОЙ АСТМОЙ

Э.Б. Белан, Е.М. Никифорова, Т.Е. Заячникова, И.Н. Шишиморов, О.В. Магницкая

Федеральное государственное бюджетное образовательное учреждение высшего образования «Волгоградский государственный медицинский университет» Министерства здравоохранения Российской Федерации
400131, Россия, г. Волгоград, площадь Павших Борцов, д. 1

E-mail: belan.eleonora@yandex.ru

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Цель: изучить клинико-иммунологическую эффективность рибомунила у детей с вирус-индуцированной бронхиальной астмой (БА).
Материалы и методы. 14 детей с вирус-индуцированной БА получали в составе комплексной терапии препарат рибомунил (3 курса, 18 месяцев); группу сравнения составили 16 больных, получавших только стандартную терапию вирус-индуцированной БА. На момент окончания исследования у детей оценивали на фоне базисной терапии БА частоту острых респираторных вирусных инфекций (ОРВИ), потребность в антибактериальной терапии, частоту определения иммуноглобулина G (IgG) к респираторно-синцитиальному вирусу (РСВ), динамику сывороточного уровня общего IgE, интерлейкина-4 (IL-4), интерферона-гамма (ИФНγ).
Результаты. Включение рибомунила в терапевтический комплекс при вирус-индуцированной БА у детей позволило в 50% случаев и 12,5% (p=0,0279) снизить потребность в базисной терапии БА. В то же время частота ОРВИ сопоставимо уменьшилась в обеих группах, однако в основной группе снизилось с 78,6% до 42,9% (p=0,0199) количество случаев, требующих назначения антибактериальной терапии. Включение рибомунила в терапевтический комплекс привело к снижению сывороточного уровня общего IgE; у больных с исходным наличием IgG к РС-вирусу снизился уровнь IL-4 и повысился уровень ИФНγ.
Заключение. Рибомунил улучшает течение вирус-индуцированной БА у детей, при этом динамика иммунологических показателей более выражена у РСВ-серопозитивных пациентов.
Ключевые слова: бронхиальная астма, дети, рибомунил, вирус-индуцированная БА
Список сокращений: БА – бронхиальная астма; ИКС – ингаляционные кортикостероиды; ИНФ – интерферон; ИЛ – интерлейкин; ОРВИ – острая респираторная вирусная инфекция; РСВ – респираторно-синтициальный вирус; Ig – иммуноглобулин; TLR – Toll-подобные рецепторы.

INTRODUCTION

Despite the significant progress made in the treatment and prevention of bronchial asthma (BA), the search for new approaches to the treatment of patients who fail to achieve a controlled course of the disease, is currently ongoing [1, 2].

Numerous epidemiological studies indicate that one of the common reasons for the development of broncho-obstructive conditions and the absence of a controlled course of asthma in children, is a respiratory tract damage. In this case, the greatest role is assigned to respiratory syncytial and rhinovirus infections [3].

In general, it is the respiratory viruses in children in 90% of cases that cause an asthma exacerbation and an increase in the severity of symptoms of the disease [4]. In addition, viral lesions of the respiratory epithelium can increase bacterial colonization and infection of the respiratory tract, increasing the need for antibacterial therapy; the greatest role in this is assigned to *Streptococcus pneumoniae, Moraxellacatarrhalis* and *Haemophilusinfluenza* [4].

The difficulty of managing patients with virus-induced broncho-obstructive diseases is due to the lack of specific antiviral therapy and prophylaxis of most of them, including respiratory syncytial viruses (RSVs) and rhinoviruses. In this regard, it seems appropriate to study the possibility of using drugs with an immunostimulating effect, the potential effectiveness of which is 40% of cases in children with recurrent respiratory tract diseases [5].

One of the most promising groups among them is represented by preparations based on bacterial lysates, which combine vaccine properties in relation to the most frequent pathogens of inflammatory diseases of the respiratory tract with a non-specific immunostimulating activity [5–8].

The latter is based on the ability of bacterial lysates to interact with a number of innate immunity structures. Thus, the induction of Toll-like TLR2/3/4 receptors causes the activation of mechanisms of (**без артикля**) antibacterial immunity [9, 29]. At the same time, a high clinical efficacy associated with the activation of macrophages (stimulation of adhesion, phagocytic activity and cytotoxicity), polinuklear cells (activation of chemotaxis, migration and adhesion), natural killer cells (activation of the antiviral effect as well as an increase in the production of gamma interferon), B-lymphocytes (with an increase in IgG, IgA and IgM titers), dendritic cells (with the synthesis reinforcement of Th1 cytokines and activation of lymphocytes) [10]. It should be borne in mind that ribosomes, the extract of which is a part of ribomunil, are 1000 times more immunogenic than whole bacteria [9, 11].

In recent studies it has nevertheless been shown that ribomunyl can induce receptors responsible for the activation of antiviral immunity, including TLR7 / 8, responsible for the induction of interferon-gamma (IFNg), and can also “cancel” the virus-mediated inhibition of TLR 9-mediated synthesis of type I INF [12].

The broad immunological activity of bacterial lysates served as the basis for their study in patients with a predisposition to perverted immune responses, in particular, in allergic diseases. Thus, in the work by Matricardi et al., an analysis of 12 placebo-controlled studies of microbial drugs in patients with allergic diseases (bronchial asthma, atopic dermatitis, allergic rhinitis) was carried out [13]. A decrease in the frequency of exacerbation and severity of symptoms was notified in half of the studies.

THE AIM of the study was to research the clinical and immunological efficacy of ribomunil in children with virus-induced BA.

MATERIALS AND METHODS

The work was carried out in the design of a prospective randomized simple comparative study in parallel groups.

The monitored parameters were:

- the need for basic therapy of BA and its volume (the stage at which a controlled course of the disease is achieved);
- a number of acute respiratory viral infections (ARVIs) per year;
- the need for ARVI antibacterial therapy (in all cases; no more than 50% of cases; not required);
- serum interleukin-4 (IL-4) levels);
- serum IFNg level;
- the presence of IgG to RSV.

The study comprised 30 children (the mean age was 4.3=0.12 years) with virus-induced BA in the disease controlled outside of ARVI with the use of pharmacotherapy corresponding to the 2nd stage (low doses of inhaled corticosteroids). The patients were managed in accordance with the Federal Clinical Guidelines "Bronchial asthma in children" and GINA 2019[1,2]. The work was performed as an initiative study with no conflict of interest. It was approved by the Regional Ethics Committee (Protocol No. 256-2016 dated 25 March, 2016). The informed consent was obtained from the legal representatives of all patients for all studies.

The inclusion criteria were as follows: the presence of foci of a chronic infection; any immunotropic therapy conducted for 6 months before the inclusion in the study.

The exclusion criteria were as follows: a refusal to participate in the study for any reason; drug intolerance.

Monitoring of the children's condition was carried out every 3 months during the entire follow–up period (with a revision of the basic therapy volume -after 1 month and 3 months).

Group 1 (n = 14) consisted of the children who were administrated, in addition to the standard BA therapy [1,2], with ribomunyl (Ribomunyl® PierreFabre; France; ATC code L03AX Other immunostimulants; Registration number: P No. 011369/01; P No. 011369/02). It was prescribed for 18 months at the dose of 0.75 mg / day according to the scheme recommended by the manufacturer (in the first month of treatment and / or daily 4 days a week for 2–5 months; 3 courses). The drug includes bacterial ribosomes as active components, titrated up to 70% of ribonucleic acids (including ribosomes *Klebsiellapneumoniae* – 3.5 shares, *Streptococcus pneumoniae* – 3.0 shares, *Streptococcus pyogenes* – 3.0 shares and *Haemophilusinfluenzae* – 0.5 shares).

Group 2 (n = 16) consisted of the children in whom a controlled course of asthma was previously achieved with the use of low doses of inhaled glucocorticosteroids as a basic therapy.

The presence of polyclonal virus-specific IgG in blood serum was detected by enzyme-linked immunoassay in accordance with the attached instructions (LLC "CNDO", St. Petersburg).

The determination of IFNg and IL-4 serum levels was performed by enzyme-linked immunoassay in accordance with the attached instructions ("CYTIMMUNE", USA; "Multiscan", Labsystem, Finland).

The determination of the total IgE level in blood serum was carried out by the enzyme-linked immunoassay method in accordance with the attached instructions (JSC "Vector-Best" (Novosibirsk); reader "Multiscan", Labsystem, Finland). If necessary, the sera were stored at –20°C for more than 2 months.

Statistical processing

To characterize quantitative indicators in the normal distribution, the arithmetic mean with a standard deviation (M±s), or the median value with an interquantile span in the nonparametric distribution (Me[Q1;Q3]), was used.

The differences between the values were considered significant at $p < 0.05$, which were determined using the Student's test for a normal distribution, Wilcoxon's test for related groups with a nonparametric distribution, Fisher's test, or X2 (depending on the sample size) to compare the frequencies.

Statistical processing of the material was carried out using the STATISTICA6.0 software package.

RESULTS AND DISCUSSION

The expediency of studying immunotropic drugs (in our study it is ribomunyl) as a part of a therapeutic complex of patients with virus-induced BA, is determined by the presence of a secondary immunodeficiency state, manifested in the recurrent nature of the infectious process, leading, among other things, to an exacerbation of asthma and / or a high frequency of bacterial complications requiring a prescription of antibacterial drugs.

In general, the course of asthma was somewhat different in the patients administrated with ribomunil, and in the comparison group.

Thus, by the end of the study, every fourth patient ($p=0.0047$) who received a standard treatment, had had its volume revised; at the same time, it had been increased in 2/16 patients, and 2/16 patients had been given a possibility to refuse it. The number of ARVI episodes had slightly decreased in patients of the both groups, which could be probably due to age characteristics, but the need for antibiotic therapy in them had remained unchanged.

The results of this study are presented in Tables 1 and 2.

The results obtained indicate that during the follow-up period, in the group of children receiving ribomunyl, the need for basic BA therapy did not increase in any case, while in the comparison group, 2 patients were prescribed the 3rd step volume therapy on the 4th and 12th months of the follow-up (Table 1).

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At the same time, the number of patients who needed basic therapy in the volume of stage 2, decreased in the main group twice (14/14, respectively, 7/14, p=0.028). However, in the comparison group, only 2 of 16 patients could refuse regular anti-asthma therapy, which was significantly less frequent than in the main group (p=0.0279) (Table 1).

In parallel with the assessment of the BA course, the number of ARVI episodes for the 1st year (Table 1) prior to the start of the research and throughout the entire follow-up period, was studied. It turned out that the incidence of diseases had significantly decreased in both groups (p=0.045), which can be explained by the age-related aspects of the pathology. However, the median value of the number of the episodes against the background of treatment was 4 in the main group and 5 in the comparison group. In addition, the number of patients who did not have ARVI complications by a bacterial infection, increased almost 3 times, and they did not need any antibiotics. These facts can be considered the evidence of the formation of more effective anti-infective resistance in the patients with virus-induced BA, if the basic therapy is supplemented with bacterial lysates, in particular, ribomunil. The data obtained are consistent with the results of a meta-analysis of 11 randomized controlled trials of ribomunil efficacy in sickly children, which has shown a 43.5% reduction in the incidence of upper respiratory tract infections [95% CI 33.7–53.2%] [29].

It has been established that at an early age, one of the most common causes of ARVI is an RSV infection. According to some authors [3, 4, 20], by the age of 5, up to 100% of children had been in contact with this type of pathogen.

At the same time, clinical manifestations of infection vary from mild diseases of the upper respiratory tract to severe lesions of the lower respiratory tract (bronchiolitis, pneumonia), accompanied by a syndrome of bronchial obstruction and virus-induced exacerbation of BA [20]. In general, in 2015, the number of registered cases of the RVC infection in the world amounted to 33.1 million people; 3.2 million patients required hospitalization; the total number of deaths in hospital was 59.600 and 149.400 outside it [21]. Up to 80% of ARVI-associated broncho-obstructive syndromes in preschoolers, is believed to be associated with this pathogen [3, 4, 17], and the annual pharmacoeconomic losses due to the RSV infection are estimated at 50–57 million pounds sterling and are associated with the incidence of preschool children [22].

In the present study, all the groups were comparable to each other in terms of the detection frequency of IgG to RSV (Table 2).

When evaluating the pharmacodynamic effects of ribomunyl, some dependence of the results on the initial presence of IgG to RSV was revealed.

In general, at the beginning of the study, antibodies were detected in 17/30 people, which corresponds to the modern data on the epidemiology of an RSV infection in children and its role in the development of BA. There were no new cases of seroconversion during the follow-up period.

During the follow-up process, in the intervention group in 4/14 cases, there was a decrease in the level of antiviral antibodies up to undetectable ones. Despite the fact that a significant difference in the frequency of the detection of antibodies to the virus (64.3%, 9/14 and 35.7%, 5/14), (p=0.14) could not be demonstrated, the achieved result can be interpreted as a trend, which needs a further study, since the number of seropositive patients in the comparison group remained unchanged (50%, 8/16). In addition, it should be borne in mind that the mechanism of the action of bacterial lysates and, in particular, ribomunyl is associated with the stimulation of the humoral link in general. This trend also deserves attention because all the children in whom IgG to RSV ceased to be detected as a result of treatment, were moved to a group that did not require a prescription of basic therapy on a regular basis, which is consistent with the data on a close relationship between the RSV infection and BA [3, 4]. Thus, in infants, the RSV infection is associated with a more than 1.5-fold risk of developing BA in the subsequent years, herewith several factors matter. First, the interferon deficiency predisposes to both a more severe course of infection and an overproduction of IgE; and, second, there is a direct damaging effect of the pathogen on the pulmonary parenchyma [23, 27, 28].

Recent studies have also shown the possibility of synthesizing antiviral IgEs, including the ones against RSV [24, 25]. Thus, the damaging role of RSV in young children is significant, especially in conditions of immunodeficiency, which creates a serious problem; it is aggravated by the extremely limited possibilities of antiviral therapy with this type of infection. Thus, palivizumab is used only for seasonal prophylaxis of severe forms in premature infants and children under 2 years of age who have been treated for bronchopulmonary dysplasia, and hemodynamically significant congenital heart defects; ribavirin is toxic and requires a reliable contraception for 7 months after treatment (in this case, when the drug is administered by inhalation, mainly for the staff and parents); type I interferon preparations are ineffective [17, 22].In this regard, immunotropic drugs are of considerable interest, since they can induce various factors of immunity, and these factors are associated with antiviral resistance. Herewith it is impossible to exclude the assumption that the activation of anti-infective defense mechanisms may contribute to the suppression of viral infection up to its eradication, explaining the decrease in serum levels of specific IgGs up to the undetectable ones in some patients.

Table 1 – Clinical efficacy of ribomunyl in children with virus-induced BA

	Group 1 (n=14)		Group 2 (n=16)	
	Before	After	Before	After
Basic treatment of asthma: No	0	50(7/14) *1p=0,0279	0	12.5(2/16)
Step 2	100 (14/14)	50.0(7/14) *2p=0,023	100 (16/16)	75.0(12/16)
Step 3	0	0	0	12.5(2/16)
ARVI episodes/year Me[Q2;Q3]	6 [5–8]	4[3-6] *3p=0,007	6 [5–7]	5[3–6] *3p=0,034
Use of antibiotics in ARVI, % (n1/n)				
No use of antibiotics	21.4(3/14)	57.1(8/14) *p=0,0199	25,0(4/16)	37.5(6/16)
In 50% cases	42.9(6/14)	28.6(4/14)	50.0(8/16)	56.3(9/16)
In 100% cases	35.7(5/14)	14.3(2/14)	25.0(4/16)	6.3(1/16)

*1p=0.0279 vs. outcomes
*2p=0.023 vs. Group 2
*3p=0.007 и *3p=0.034 vs. outcomes
n – number of children in groups
n1 – number of children with effect

Table 2 – Dynamics of immunological parameters of children with VBA against the background of treatment with ribomunil

	Group 1 (n=14)		Group 2 (n=16)	
	IgGк PCB+(n=9)	IgGк PCB-(n=5)	IgGк PCB+(n=8)	IgGк PCB-(n=8)
IgE, ME/ml Me[Q1;Q3]	176[119; 312]	132[87; 460]	112[86; 556]	154[121; 339]
	141[90; 288]*1	107[69; 181]* 2	124[59; 358]	148[109; 411]
ИФНg, pg/ml Me[Q2;Q3]	1.43[0; 3.01]	6.1[3.8; 10.5]	2.4[0; 4.1]	3.2[0; 5.9]
	2.2[1.8; 7.2] * 4	6.2[4.2; 12.9] * 3	3.2[2.1;5.4] * 5	3.9[3.1; 8.7]
IL-4, pg/ml Me[Q2;Q3]	14.4[2.1; 19.0]	8.8[3.6; 98.0]	15.6[0; 44.7]	12.2[6,1; 24.6]
	12.1[0; 17.1] *6	10.4[3.1; 69.1]	17.8[0; 36.5]	10.8[0; 59.5]

* 1 p=0.008 in comparison with initial level
* 2p=0.012 in comparison with initial level
* 3p=0.038 in comparison with initial level
* 4p=0.022 in comparison with initial level
* 5p=0.014 in comparison with initial level
* 6p=0.047 in comparison with initial level
IgG to RSV + – children with detectable level of IgG to RSV
IgG to RSV – –children with undetectable level of IgG to RSV

At the same time, there is evidence that bacterial lysates have not only an immunostimulating effect but can also change the phenotype of the Tr-cell response towards the Th1 variant.

As for the immunological parameters, the serum levels of total IgE, IL-4 and IFNg were assessed in this work (Table 2).

In this study, the integral indicator of atopy – the serum level of total IgE – was, in general, typical for patients with this type of pathology, and its dynamics did not depend on the presence of IgG to RSV, but it was different in the groups with different kinds of treatment. Thus, in the patients of the main group in the combination of BA and RSV infection, the serum level of total IgE decreased from Me176 [Q2; Q3 119; 312] IU / ml to Me141 [Q2; Q3 90; 288] IU / ml (p = 0.008), and among the uninfected participants it decreased from Me132 [Q2; Q3 87; 460] IU / ml to Me107 [Q2; Q3 69; 181] IU / ml (p = 0.012). At the same time, in the group of patients who had not received additional therapy, the dynamics of the total IgE serum level had not been registered by the end of the study (Table 2).

Despite the multiplicity of immunological mechanisms that determine the Th2 phenotype of the response and control allergic inflammation, IL-4 and IFNg are the main regulatory cytokines for IgE.

In general, the first one is the key cytokine produced primarily by CD4+Th2-lymphocytes, mast cells, and basophils [31]. It induces not only the production of IgE, but also the expression of molecules of the main histocompatibility complex of class II, B7 and CD40 receptors, as well as membrane IgM on the surface of B-lymphocytes, thereby increasing the capabilities of antigen-presenting cells. Being one of the regulators of allergic inflammation, IL-4 in asthma is involved in the remodeling of the respiratory tract and the activity stimulation of mucous-producing cells [32]. Hyper-expression of the IL-4 gene in the lung triggers eosinophilic inflammation without developing hyperresponsiveness of the respiratory tract. It is known that an increase in the IL-4 / IFNg ratio in the broncho-alveolar fluid is usually accompanied by an increase in the number of Th2 lymphocytes in the respiratory tract, which is associated with a more severe course of asthma in children [33]. Along with the

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level of IL-5, IFNg, GM-CSF (granulocyte-macrophage colony-stimulating factor), IL-4 parameters are significant biomarkers of the severity of allergic diseases, including BA [31].

In the present study, a decrease in the serum IL-4 level (from Me14.4 [Q2; Q3 2.1; 19.0] pg/ml to Me12.1 [Q2; Q3 0; 17.1] pg/ml (p=0.047) was observed only among the children with a combination of BA and RSV infection. At the same time, attention is drawn to the fact that by the end of the study, 3/9 of the participants in this subgroup had undetectable cytokine levels (Table 2).

The second important cytokine that affects the IgE synthesis, but has an effect opposite to IL-4, is IFNg. The main producers of this cytokine are T-lymphocytes (mainly the Th1 subpopulation), natural killers (NKs), natural-killer T-cells (NKT cells) and antigen-presenting cells (macrophages and dendritic ones), as well as B-lymphocytes. Moreover, its origin plays a role in the implementation of various immune responses. Thus, IFNg secreted by NKT cells, is of the greatest importance in the induction of an early protection and autocrine regulation; the T-lymphocytic cytokine is the most important in the implementation of the mechanisms of adaptive immunity [30], in particular, in the eradication of infectious agents and mutated cells, etc. The central effector role of IFNg is determined by its ability to regulate the activity of the T-cell link, which provides multiple anti-infective mechanisms. It is important that an increase in the production of endogenous IFNg promotes the activation of not only antiviral, but also antibacterial and anti-chlamydial defense [30].

Initially, the serum IFNg level in children in the both groups did not differ and, in general, was Me 3.6 [Q2; Q3 1.0-4.1] pg/ml (the results for subgroups are shown in Table 2). Nevertheless, it turned out that the children seropositive for RSV (18/30), had values of this indicator <3.6 pg/ml (72.2% vs 33.3%, p=0.026) significantly more often.

The dynamics of the content of this biomarker in the blood serum of the children who received only standard BA therapy, was observed only in the subgroup of the children with serological markers of infection, in whom, on average, it increased by 8% from Me2.4 [Q2; Q30; 4.1] pg/ml up to Me3.2 [Q2; Q3 2.1; 5.4] pg/ml (p=0.014), while there was no such dynamics in the subgroup of seronegative patients. At the end of the study, the children of the main group showed a significant increase in IFNg both in the group of RSV-seropositive patients and in the absence of serological markers of the infection, respectively, Me1.43 [Q2; Q30; 3.01] pg/ml and Me2.2 [Q2; Q31.8; 7.2] pg/ml (p=0.022) in the first subgroup and Me 6.1 [Q2; Q3 3.8; 10.5] pg / ml and Me6.2 [Q2; Q3 4, 2; 12.9] pg/ml (p=0.014) in the second one (Table 2).

Bacterial lysates are currently considered one of the most promising groups of immunomodulators in sickly children 5]. In addition, it is known that the inclusion of bacterial lysates in the complex therapy of children with moderate asthma, can help restore IFNg production to the level of healthy children and lead to a significant decrease in the total IgE serum level [14]. The ability of bacterial lysates to promote the Th1 phenotype of the immune response, including patients with allergic diseases, has been described by a number of other authors. In particular, a similar immunomodulatory effect has been shown for ribomunyl [12, 13, 15, 16]. In the study by Bystron J., thirteen adult patients with seasonal rhinoconjunctivitis received ribomunil according to the recommended regimen for 3 months (from April to June), after which they were followed up for 2 months. By the 3rd month, in the group who had received the drug, the level of IFNg had significantly increased by 30%, and by the 5th month 5 – by 37%, while the dynamics was more pronounced (65%) among the patients with clinical improvement. An increase in the production of this cytokine correlated with an increase in the serum level of macrophage IL-12. During the study, there was not a single case of deterioration of a patient's condition [15].

The relationship of RSV infection with the IFNg system is also known; in particular, there is evidence that severe forms of RSV infection are associated with impaired IFNg production [3]. This study shows some product differences associated with RSV. Thus, only in the children seropositive for RSV, the serum level of this cytokine significantly increased as a result of treatment (p<0.05), while in uninfected children it remained unchanged. These studies are consistent with the results obtained by other authors for children with atopic pathology and indicate the ability of bacterial lysates to exert pro-Th1 and anti-Th2 effects. Considering that the Th2 phenotype of the immune response is one of the key mechanisms for the development of bronchial hyperreactivity during exacerbation of asthma, the shown effect is important for the patients with this type of pathology.

Despite the fact that the drugs based on IFNg are currently developed, their therapeutic potential, unfortunately, is extremely limited not only by a very high cost of treatment, but also by serious side effects, in particular, influenza-like syndrome, lethargy, cough, depressive conditions, etc. [30]. Today, this makes them unacceptable for use in the children with virus-induced BA and determines the relevance of the search for other directions of therapy. They can be the elimination of the causes leading to the suppression of the synthesis of endogenous interferon, with the aim of their possible elimination, as well as the search for ways to overcome them with the help of drugs having immunomodulatory effects.

During therapy, negative dynamics of the serum IL-4 level also took place only in RSV-positive children. In RSV negative children, as well as in the children of the comparison group, the cytokine level remained at the initial level.

In general, the effect of ribomunyl in viral-induced BA can be represented as follows. The first direction is associated with the antigen-independent activation of differentiation and proliferation of cells of the immune system through the mechanisms of innate immunity. As a mixture of bacterial proteoglycans and ribosomes, the drug reaches the lymphoid cells in Peyer's glands and stimulates the maturation of regional dendritic cells. There are not many data on the effect of the drug on the mechanisms of innate immunity [9,10,29], some of them provide evidence of an increase in the expression of adhesion molecules and phagocytic activity of peripheral blood neutrophils [6].

The dendritic cells activated by the drug, stimulate T-lymphocytes to produce Th1-dependent cytokines, including IFNg, thus enhancing the cytotoxic properties of the body, including the antiviral activity. Moreover, the oral route of the drug administration and the induction of lymphocytic cells of Peyer's glands cause the expansion of B-cells and the production of secretory IgA, as well as serum IgG and IgM, which has been justified for the children with recurrent respiratory infections [16]. In addition, other studies have shown that in volunteers, increased serum IgA levels were associated with decreased adhesion of Streptococcus pneumoniae [16].

The second direction is associated with the induction of acquired antigen-dependent specific immunity. In fact, it is vaccination against pathogens of respiratory infections, the components of which are a part of the drug. It has been shown that their immunogenicity practically does not differ from the antigenic determinants of the native pathogen [29].

It should be borne in mind that many pathogens, including opportunistic ones, have an immunosuppressive effect of their own; therefore, the suppression of their reproduction may have an indirect immunostimulating effect [8].

Within the framework of this study, the microbial composition and microbial-viral associations that led to an exacerbation of asthma in children and necessitated antibiotic therapy were not under discussion, however, it can be assumed that the results obtained are associated with the complex effect of ribomunyl on the immune system.

CONCLUSION

Thus, the inclusion of ribomunyl in the complex therapy of children with virus-induced BA, leads to an improvement in the course of both the underlying disease and a decrease in the frequency and severity of ARVI episodes. The results achieved are consistent with the dynamics of immunological parameters, which turned out to be more pronounced in RS-virus infected children. Considering the fact that bacterial lysates, inducing the synthesis of antibacterial antibodies, do not possess their own antiviral properties, it can be assumed that the suppression of viral infection is associated with the immunomodulatory properties of the drug.

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AUTHORS' CONTRIBUTION

All the authors have contributed equally to the research work.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. [Federal'nye klinicheskie rekomendacii «Bronhial'naja astma u detej]. Moscow. 2019. 76p. Russian
2. The Global Asthma Report 2018. Available from: http://globalasthmareport.org/Global Asthma Report 2018.pdf (date of the application: 2019 March 22). Russian
3. Le Souëf P. Viral infections in wheezing disorders. European Respiratory Review. 2018;27:170133. DOI: 10.1183/16000617.0133-2017.
4. Mikhail I, Grason M. Asthma and viral infections: An intricate relationship. Annals of Allergy, Asthma & Immunology. 2019;123(4):352–358. DOI: 10.1016/j.anai.2019.06.020.
5. Del-Rio-Navarro BE, Espinosa-Rosales FJ, Flenady V, Sienra-Monge JJL. Cochrane Review: Immunostimulants for preventing respiratory tract infection in children. Evidence-Based Child Health: A Cochrane Review Journal. 2012;7(2):629–717. DOI: 10.1002/ebch.1833.
6. Esposito S, Soto-Martinez EM, Feleszko W, Jones MH, Kun-Ling Shen, Schaad Urs B. Nonspecific immunomodulators for recurrent respiratory tract infections, wheezing and asthma in children: a systematic review of mechanistic and clinical evidence. Current Opinion in Allergy and Clinical Immunology. 2018;18(3):198–209. DOI: 10.1097/ACI.0000000000000433.
7. Esposito S, Bianchini S, Polinori I, Principi N. Impact of OM-85 Given during Two Consecutive Years to Children with a History of Recurrent Respiratory Tract Infections: A Retrospective Study. International Journal of Environmental Research and Public Health. 2019;16(6):1065. DOI: 10.3390/ijerph16061065.
8. Hamill P, Brown K, Jenssen H, Hancock RE. Novel anti-infectives: is host defence the answer? Current Opinion in Biotechnology. 2008;19(6):628–636. DOI: 10.1016/j.copbio.2008.10.006.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2020-8-3-160-168

9. Tejera-Alhambra M, Palomares O, Perez de Diego R, Diaz-Lezcano I, Sanchez-Ramon S. New Biological Insights in the Immunomodulatory Effects of Mucosal Polybacterial Vaccines in Clinical Practice. Current Pharmaceutcal Design. 2016;22(41):6283–6293. DOI: 10.2174/1381612822666160829143129.
10. [PRIMA: pediatricheskie rekomendacii po immunomodulirujushhim preparatam v ambulatornoj praktike: (konsensus) / Pediatr. respirator. o-vo, Ros. assoc. allergologov i klinich. immunologov, Mosk. o-vo det. vrachej, Federacija pediatrov stran SNG [i dr.]. 2-e izd., pererab. i dop.] Moscow.: RG-Press. 2017. 76 p. Russian
11. Herberhold S, Coch C, Zillinger T, Hommertgen B, Busch N, Schuberth C, Hartmann E, Wimmenauer V, Hagmann CA, Lüdenbach B, Schlee M, Bootz F, Hartmann G, Barchet W. Delivery with polycations extends the immunostimulant Ribomunyl into a potent antiviral Toll-like receptor 7/8 agonist. Antiviral Therapy. 2011;16(5):751–758. DOI: 10.3851/IMP1822.
12. Lynch JP, Mazzone SB, Rogers MJ, Arikkatt JJ, Loh Z, Pritchard AL, Upham JW, Phipps S. The plasmacytoid dendritic cell: at the cross-roads in asthma. European Respiratory Journal. 2014;43(1):264–275. DOI: 10.1183/09031936.00203412.
13. Matricardi PM, Bjorksten B, Bonini S, Bousquet J, Djukanovic R, Dreborg S, Gereda J, Malling H.-J, Popov T, Raz E, Renz H. Microbial products in allergy prevention and therapy. Allergy. 2003;58:461–471. DOI: 10.1034/j.1398-9995.2003.00175.x.
14. Prosekova EV, Derkach VV, Shestovskaja TN, Sergienko IS. [Vlijanie bronhomunala na citokinovyj profil' syvorotki krovi detej s bronhial'noj astmoj. Aktual'nye voprosy allergicheskih zabolevanij: sb. tezisov III Regional'noj nauchno-prakticheskoj konferencii]. Vladivostok, 2005:58p. Russian
15. Bystron J, Hermanova Z, Szotkovska J, Heller L, Pazderova D. Effect of Ribosomal Immunotherapy on the Clinical Condition and Plasma Levels of Cytokines IL-4, IL-5, IL-12 and IFNgamma and Total IgE in Patients with Seasonal Allergy during the Pollen Season. Clinical Drug Investigation. 2004;24(12):761–764. DOI: 10.2165/00044011-200424120-00007.
16. Hbabi-Haddioui L, Roques C. Inhibition of Streptococcus pneumonia adhesion by specific salivary IgA after oral immunostimulation with a ribosomal immunostimulant. Drugs. 1997;54:29–32. DOI: 10.2165/00003495-199700541-00008.
17. Barr R, Green CA, Sande CJ, Drysdale SB. Respiratory syncytial virus: diagnosis, prevention and management. Therapeutic Advances in Infectious Disease. 2019;6:2049936119865798. DOI: 10.1177/2049936119865798.
18. Green CA, Yeates D, Goldacre A, Sande C, Parslow RC, McShane P, Pollard AJ, Goldacre MJ. Admission to hospital for bronchiolitis in England: trends over five decades, geographical variation and association with perinatal characteristics and subsequent asthma. Archives of Disease in Childhood. 2016;101(2):140–146. DOI: 10.1136/archdischild-2015-308723.
19. Ralston SL, Lieberthal AS, Meissner HC. et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. Pediatrics. 2014;134(5):e1474–e1502. DOI: 10.1542/peds.2014-2742.
20. Bont L, Checchia PA, Fauroux B, Figueras-Aloy J, Manzoni P, Paes B, Simões EA, Carbonell-Estrany X. Defining the Epidemiology and Burden of Severe Respiratory Syncytial Virus Infection Among Infants and Children in Western Countries. Infectious Diseases and Therapy. 2016;5(3):271–298. DOI: 10.1007/s40121-016-0123-0.
21. Shi T, McAllister DA, O'Brien KL. et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet. 2017;390(10098):946–958. DOI: 10.1016/S0140-6736(17)30938-8.
22. Cromer D, van Hoek AJ, Newall AT, Polard AJ, Jit M. Burden of paediatric respiratory syncytial virus disease and potential effect of different immunisation strategies: a modelling and costeffectiveness analysis for England. The Lancet Public Health. 2017;2(8):e367–e374. DOI: 10.1016/S2468-2667(17)30103-2.
23. Rosas-Salazar C, Gebretsadik T, Anderson LJ, Jadhao S, Chappell JD, Larkin EK, Martin L. Moore ML, Peebles RS, Hartert T. Risk or Protective Factor? Mild Respiratory Syncytial Virus Infection in Infancy and the Development of Recurrent Childhood Wheeze. American Journal of Respiratory and Critical Care Medicine. 2020;201:A5028. DOI: 10.1177/2049936119865798.
24. Teach SJ, Gill MA, Togias A, Sorkness CA, Arbes SJ. Jr. et al. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. The Journal of Allergy and Clinical Immunology. 2015;136(6):1476–1485. DOI: 10.1016/j.jaci.2015.09.008.
25. Tam JS, Jackson WT, Hunter D, Proud D, Grayson MH. Rhinovirus specific IgE can be detected in human sera. Journal of Allergy and Clinical Immunology. 2013;132(5):1241–1243. DOI: 10.1016/j.jaci.2013.07.011.
26. Glaser L, Coulter PJ, Shields M, Touzelet O, Power UF, Broadbent L. Airway Epithelial Derived Cytokines and Chemokines and Their Role in the Immune Response to Respiratory Syncytial Virus Infection. Pathogens. 2019;8(3):106. DOI: 10.3390/pathogens8030106.
27. Bermejo-Martin JF, Garcia-Arevalo MC, De Lejarazu RO, Ardura J, Eiros JM, Alonso A, Matías V, Pino M, Bernardo D, Arranz E, Blanco-Quiros A. Predominance of Th2 cytokines, CXC chemokines and innate immunity mediators at the mucosal level during severe respiratory syncytial virus infection in children. European Cytokine Network. 2007;18(3):162–167. DOI: 10.1684/ecn.2007.0096.
28. Kaneko H, Matsui E, Asano T, Kato Z, Teramoto T, Aoki M, Kawamoto N, Lian LA, Kasahara K, Kondo N. Suppression of IFN-gamma production in atopic group at the acute phase of RSV infection. Pediatriac Allergy and Immunology. 2006;17(5):370–375. DOI: 10.1111/j.1399-3038.2006.00419.x.
29. Zaplatnikov AL, Girina AA, Lepsieva IV, Korovina NA, Cheburkin AA, Svintsitskaya VI, Coroid NV. Ribosomal immunotherapy in children with recurrent infections and chronic respiratory diseases: preventive and economic efficacy. Pediatria. 2017;96(2):151–157.
30. Kak G, Raza M, Tiwari BK. Interferon-gamma (IFN-γ): Exploring its implications in infectious diseases. Biomolecular Concepts. 2018;9(1):64–79. DOI: 10.1515/bmc-2018-0007.
31. Hatami H, Ghaffari N, Ghaffari J, Rafatpanah H. Role of Cy-

tokines and Chemokines in the Outcome of Children with Severe Asthma: Narrative Review. Journal of Pediatrics Review. 2019;7(1):17–28. DOI: 10.32598/jpr.7.1.17.

32. Hussein YM, Alzahrani SS, Alharthi AA, Ghonaim MM, Alhazmi AS, Eed EM, Shalaby SM. Association of serum cytokines levels, interleukin 10 -1082G/A and interferon-γ +874T/A polymorphisms with atopic asthma children from Saudi Arabia. Cellular Immunology. 2014;289(1–2):21–26. DOI: 10.1016/j.cellimm.2014.03.006.

33. Keskin O, Keskin M, Kucukosmanoglu E, Ozkars M.Y, Gogebakan B, Kul S, Bayram H, Coskun Y. Exhaled RANTES and interleukin 4 levels after exercise challenge in children with asthma. Annals of Allergy Asthma & immunology. 2012;109(5):303–308. DOI: 10.1016/j.anai.2012.08.009.

AUTHORS

Eleonora B. Belan – Doctor of Sciences (Medicine), Professor, the Head of the Department of Immunology and Allergology of Volgograd State Medical University. ORCID: 0000-0003-2674-4289. E-mail: belan.eleonora@yandex.ru

Elizaveta M. Nikiforova – Candidate of Sciences (Medicine), Associate Professor, Associate Professor of the Department of Immunology and Allergology of Volgograd State Medical University. ORCID: 0000-0003-1475-9301. E-mail: maior10@yandex.ru

Tatyana E. Zayachnikova – Doctor of Sciences (Medicine), Associate Professor, Professor of the Department of Pediatrics and Neonatology of the Institute of Continuous Medical and Pharmaceutical Education of Volgograd State Medical University. ORCID:0000-0001-6758-4686. E-mail: guz5deti@mail.ru

Ivan N. Shishimorov – Doctor of Sciences (Medicine), Associate Professor, the Head of the Department of Pediatrics and Neonatology of the Institute of Continuous Medical and Pharmaceutical Education of Volgograd State Medical University. ORCID: 0000-0001-6098-7028. E-mail: drshishimorov@gmail.com

Olga V. Magnitskaya – Doctor of Sciences (Medicine), Associate Professor, Professor of the Department of Pediatrics and Neonatology of the Institute of Continuing Medical and Pharmaceutical Education of Volgograd State Medical University. ORCID: 0000-0001-6670-9029. E-mail: magol73@ya.ru