THE CYTOKINE STATUS AND IMMUNOCORRECTING THERAPY FOR CHILDREN OF PRESCHOOL AGE WITH BRONCHOPULMONARY PATHOLOGY

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Background

The incidence of the diseases of the respiratory system remains a major clinical problem for the modern pediatrics. This is reflected by the high level of children morbidity, infant mortality as well as disability at the adolescent age (Alimov, 2003). In early diagnostics and prevention of progressing pathology the special place is allocated to the risk factors, playing important role in genesis of diseases and under certain conditions they can have key meaning in the prognosis of pathological process (Baranov, Sheplyagina, Ilyin et al., 2005; Samsigina, 2005). At present time there are data about impact of unfavorable ecological environment on the prevalence of some diseases (Samsigina et al., 2010; Larrieu, Lefranc, Gault, Chatignoux, Couvy, Jouves, and Filleul, 2009). At the same time, there is a poorly investigated issue on prevalence of respiratory system chronic diseases of allergic and infectious-inflammatory origin in children and adolescents living in Aral area (Alimukhamedova, 1998; Djubatova and Umarova, 2001; Kuanova, 1999).

The development of immune insufficiency in children of preschool age with bronchopulmonary pathology results in development of bacterial complications and stratification of viral infections, and, in opinion of the practicing doctors and researchers, considerably worsens the prognosis of disease (Djubatova and Umarova, 2001; Kuanova, 1999). Currently, the studies are carried out on parameters of immune response in this category of children (Alimukhamedova, 1998; Mazhitova, Isaeva, Choy, and Mergenova, 2005; Albitskiy and Baranov, 1986). Last years the growing interest to cytokine part of the immune response in children of preschool age with bronchopulmonary pathology in the majority of the countries of the world is connected with insufficient protective efficiency of antibacterial therapy, and also with opportunities of medicamentous immunocorrection (Alimukhamedova, 1998).

In the complex immune mechanisms cytokines perform the basic regulatory function - mediators of intercellular interactions. Proinflammatory cytokines are produced and effect on the immunocompetent cells, initiating inflammatory response (Di Renzo, Pasqui,
Bruni, Saletti, Bova, Chiarion, Girardello, Ferri, and Auteri, 1997). This group includes IL-1, IL-6, IL-8, IL-12, IFN\(\alpha\), IFN\(\gamma\), TNF\(\alpha\). Many authors note that the high level of cytokines, first of all, proinflammatory, is the reflection of activity and severity of pathological process (Mazhitova, Isaeva, Choy, and Mergenova, 2005; Albitskiy and Baranov, 1986). It is known that TNF\(\alpha\) is multipotent cytokine which is basically produced by monocytes and macrophages and carries out major functions. During onset of inflammation it activates endothelium, raises expression of adhesive molecules on the endothelial cells and promotes leukocyte adhesion to the endothelium, activates leukocytes (granulocytes, monocytes, lymphocytes), induced production of other proinflammatory cytokines, having synergic action with TNF\(\alpha\): IL-1, IL-6, IL-8, IFN-\(\alpha\), GM-CSF (Anonym, 2002; Sentsova and Revyakina, 2006). IL-8 is synthesized mainly by monocytes, macrophages and neutrophils. The most important biological function of TNF\(\alpha\) cytokine is selective for neutrophils highest chemoattractant activity. IL-4 strengthens neutrophil adhesion to endothelium and their exocytosis (degranulation), initiates respiratory burst, causes massive infiltration of neutrophil tissue (Kuanova, 1999; Illeni, Bombelli, Poli, and Pattarino, 1991). Thus, it is possible to assess indirectly activity of proinflammatory process as a whole.

Therefore, the prime task in rehabilitation of such children is the orientation of therapy to decrease intensity of antigen influence (sanitation of foci of chronic infection, restoration of integrity of epithelial layer of the respiratory tract) and increase in resistance of microorganisms in order to increase efficacy of the defensive immune factors. Imunorix is the preparation of choice. Stimulating phagocytary activity of granulocytes and macrophages, Imunorix inhibits reproduction and promotes eradication of such microorganisms as Staphylococcus aureus, hemolytic staphylococcus, fungi etc. In particular, it was shown, that Imunorix enhanced chemotaxis of phagocytes and cytotoxic activity of the natural cell-killers; increased lymphocyte proliferation; normalized the balance between T-helpers and T-suppressors; stimulates producing IL-2 and expression of specific receptors by lymphocytes, production of gamma-interferon and formation of antibodies (SIgA) (Uchaykin, Kladova, and Bevza, 2008; Sentsova and Revyakina, 2006). Imunorix advantages include minimal quantity of the adverse effects and opportunity of application in the pediatric practice.

The purpose of the present work was the analysis of the contents of serum proinflammatory cytokines TNF\(\alpha\), IL-1\(\beta\) and IL-4 in children with bronchopulmonary pathology as well as immunocorrection by drug Imunorix.

**Materials and methods**

In a course of the present research we carried out clinical-laboratory examination of 70 children of the age from 3 to 7 years living in the Khorezm area. All children were observed and examined under the common standard clinical conditions. The control group of 40 practically healthy children of the same age was also under observation. Totally 110 children were participated in this study. The parents of the participants of this investigation gave informed consent for performance of the investigation of the cytokine status in children.

Criteria for inclusion in study group was the age and number of episodes of acute respiratory diseases per one year: 5 and more episodes at the age of from 3 till 5 years, 4 and more at the age of from 5 till 7 years (on the basis of criteria offered by A.A.Baranov and V.Yu.Albitskiy). These children were divided into 3 groups as follows: group I (n=35) included children with acute bronchitis during exacerbation period; group II (n=35) included also children with chronic bronchitis at the stage of remission; control group (n=40) comprised of healthy children of the age from 3 to 7 years. Criteria of exclusion were presented by any autoimmune and allergic diseases, which could impact significantly on the function of immune system. The children from group 1 were prescribed Imunorix immediately after stopping of catarrhal symptoms, and children
from group 2 received Imunorix during period of active observation. Immunological examination was performed before treatment and 10 days after the last receiving of preparation. Imunorix is manufactured by “Polychem S.A., (Luxembourg)”. Pharmacological group presents by immunomodulating means. Code ATX: LO3AX05. The international not patented name (INN): Pidotimod. The active substance of preparation Imunorix is a high-purified synthetic substance of dipeptide nature working through regulation of immune response. Pidotimod is prescribed in dose 400 mg (1 bottle) twice a day for 15 days outside the periods of eating.

Concentration of cytokines: IL-1β and IL-4, and TNF-alpha were determined by method of immunoenzymatic analysis with use of the Kits of reagents manufactured by Limited Company “Cytokin” (St.-Petersburg Research Institute of Highly Purified Biopreparations) in the group of immunomorphology of the Institute of Immunology of the Academy of Sciences of the Republic of Uzbekistan.

Statistical analysis of the results obtained was performed with use of the software for statistical data processing Statistica®, version 6.0. Reliability of differences between compared groups was estimated by Student’s criteria. The differences of the comparative values were considered as reliable at p<0.05.

**Results**

To the humoral factors of immunity can be also related cytokines, mediators of non-immunoglobulin nature, responsible for interaction between cells during immune response.

We have established that in children from group 1 spontaneously monocytes produced reliably more IL-1β than in children from control group (88.2±5.1 pg/ml vs. 62.5±2.3 pg/ml ; p<0.001), and reliably more than in children with chronic bronchitis outside of the period of maximum activity of ARI (50.9±1.8 pg/ml, p< 0.01) (Table 1). The level IL-4 in children during an episode of ARI aggravation was reliably reduced (19.7±0.6 pg/ml vs. 24.1±1.6 pg/ml, p < 0.05), in studied children from group 2 the decrease of this parameter was not reliable (21.3±0.9 pg/ml). Our investigation has disadvantage because of small number of children we failed to obtain reliability of these parameters. The similar tendency was observed during study the level of TNF-α, p<0.001.

**Table 1. The cytokine status, М±М**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group II</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β, pg/ml</td>
<td>88.2 ± 5.1***</td>
<td>50.9 ± 1.8**</td>
<td>62.5 ± 2.3</td>
</tr>
<tr>
<td>IL-4, pg/ml</td>
<td>19.7 ± 0.6*</td>
<td>21.3 ± 0.9</td>
<td>24.1 ± 1.6</td>
</tr>
<tr>
<td>TNF-α, pg/ml</td>
<td>30.2 ± 1.1***</td>
<td>53.8 ± 2.2</td>
<td>55.6 ± 2.0</td>
</tr>
</tbody>
</table>

Note: * Reliability in relation to control group – p<0.05-0.001

Depressive dynamics of changed concentrations of IL-4 and TNF-α in the blood serum of children with bronchopulmonary pathology at the stage of exacerbation was connected to more marked expositional influence of the often and complicated episodes of recurrence of infectious process in the upper respiratory ways continuing for a long time.

Thus, in studied children with complicated bronchopulmonary pathology the secondary immunologic insufficiency has been developed, that is the basis for application of preparations having immunocorrecting effects.

The therapy with Imunorix resulted in significant correction of the IL-1β level, and more expressed dynamics was observed in group 1 of studied patients (61.7±3.7 pg/ml vs. 88.2±5.1 pg/ml before treatment). The level of TNF-alpha, having positive dynamics, has raised practically 1.5 times, but has not reached parameters of control group
(30.2±1.1 pg/ml before treatment against 49.7±1.1 pg/ml after treatment in comparison with control values - 55.6±2.0 pg/ml, p< 0.01).

Dynamics of change of the level IL-4 after the course of treatment with Imunorix was positive in studied groups I and II, however, it was more intensive in group 1 (19.7±0.6 pg/ml before use of Imunorix and 22.9±0.8 pg/ml after treatment, p<0.05) in group II these values were 21.3±0.9 pg/ml before treatment and 22.8±1.7 after correction.

**Conclusion**

The results of the investigations performed have shown that the use of Imunorix, having immunocorrecting activity induced structural changes in the immune system and by that resulted in reduction of morbidity rate; decrease in number of children from the group of frequent and long illness; shortening and attenuating of severity of disease, practically absence of the adverse effects. An opportunity to provide activating effect on various types of immunity (congenital and adaptive immune response) allows to consider this preparation as innovational immunomodulator with unique for today multi-directed mechanism of action.

The data obtained in our study about cytokine status in children and its correction with preparation Imunorix in children of preschool age required correction of the changes presented in the immunity and strengthening of the health of the growing generation. Consequently the further investigations will be justified to develop approaches for improvement of the well-being of children taking into account the state of immune system.

**References**


