Features of the immune status in patients with chronic and complicated pyodermas: choice of a therapeutic correction method

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Abstract

Introduction: To compare the features of the immune status in patients with chronic and complicated pyoderma in the course of complex pharmacotherapy using immunomodulators based on transfer factors and glucosaminylmuramyldipeptide.

Materials and methods: A clinical examination of 107 patients with pyoderma, divided into three groups, was carried out. All individuals underwent immunological examination before and after etiopathogenetic treatment. The patients of the first group were additionally treated with a drug containing signaling immunoactive molecules (transfer factor) as an immunomodulator; the patients of the second group received glucosaminylmuramyldipeptide; and the patients of the third group received standard antibacterial therapy.

Results and discussion: Prior to the beginning of pathogenetic therapy, the patients were found to lack non-specific mechanisms of antimicrobial protection; there was a decrease in the activity and intensity of phagocytosis: phagocytic index and phagocytic number of neutrophils by 1.2 and 1.3 times; the production of proinflammatory cytokines IL-6 increased by 2.3 times, IL-8 – by 2.1 times, and TNFa – by 2.4 times. The study of immunological parameters after the inclusion of immunomodulators into the therapy revealed an increase in the phagocytic activity of neutrophils, and the indicators of the NST test were close to the control ones. The production of proinflammatory cytokines in the blood serum was restored to the level of the healthy individuals. Normalization of the number of CD4⁺, CD8⁺, CD19⁺ cells was observed in 86.0 ± 3% of the patients. At the same time, against the background of the use of glucosaminylmuramyldipeptide, a more intensive recovery of all links of anti-infectious immunity was recorded in comparison with the group where transfer factor molecules were used.

Conclusion: A drug based on glucosaminylmuramyldipeptide can be recommended as the drug of choice in non-specific immunocorrection for complex pharmacotherapy of pyoderma accompanied by secondary immune insufficiency, in comparison with a drug containing transfer factors.

Keywords

pyoderma, immunity, immunotropic drugs, clinic, treatment.
Introduction

In recent decades, there has been a growing number of complicated and chronic forms of an infectious inflammatory process (Blakhnina 2010).

When analyzing factors which influence the course of pyoderma and the choice of treatment tactics, it is important to understand that along with pathogenicity and resistance of infecting agents (Jansen et al. 2014), internal causes are also of importance as they reduce a skin barrier function, which leads to complications of pyogenic infections (Leyden et al. 2007; Belkova and Rachina 2012; Murashkin 2013; Stevens et al. 2014). One of the reasons for a chronic course of pyoderma is a change in immunogenicity of the organism as a result of endogenic toxicosis and consecutive opportunistic pathogenic microflora (Chen and Tsao 2013; Goltser et al. 2015; Samtsov et al. 2018). It is followed by a disrupted activity of polymorphonuclear leukocytes, a decreased activity of T-cells, a changed T-cell subset distribution, and a changed cellular immunologic response (first of all, phagocytic activity of macrophages and complete phagocytosis) (Stalberg et al. 2002; Khaitov 2018).

The first phase of the immune response to infection is phagocytosis of the microorganism followed by intracellular digestion. Basic phagocytic cells are polymorphonuclear neutrophils and macrophages. A chain of enzymatic reactions facilitates activation of non-specific factors of the humoral component of the immune system – a complement factor, which increases polymorphonuclear leukocytes chemotaxis along with the absorption activity of macrophages. Leukocyte influx induces potent and acute antimicrobial inflammatory response (Mikheev et al. 2017; Khaitov 2018; Khaitov 2020).

Cell mediators (cytokines) are actively involved in the activation of macrophages, phagocytosis of microbes and presentation of antigens to T-cells. It is also established that in the first phase of the immune response, a macrophage is activated both due to its own cytokines (IL-1) and cytokines secreted by Th0 lymphocytes (macrophage activating factor, IL-2, IL-4; IFN-α, IFN-γ). It is believed that it is this complex of cytokines that induces the expression of class 2 antigens of the major histocompatibility complex (MHC) on the membranes of antigen-presenting cells. By binding to cellular antigens, macrophages and other antigen-presenting cells present them to null cells to trigger a specific phase of the immune response (Khaitov 2018).

There is no activation of the monocyte-macrophage phase in case of chronic infectious diseases and, therefore, there is no presentation of the complex (antigen in combination with the class 2 MHC determinant) to Th0 lymphocytes, followed by a specific phase of the immune response, all this happening along with a failure of natural killer cells (Matalon et al. 2016; Khaitov 2018).

Treatment of pyoderma means not only the use of antibacterial drugs, but also various methods of specific and nonspecific immunotherapy. Among them are such methods as a soluble antigen complex (antifagin); antistaphylococcal hyperimmune plasma; bacterial poly-saccharides (pyrogenal, sodium nucleinate); substances of microbial origin, such as toxoids, lysates of microorganisms (imudon, IRS-19), which contain peptidoglycan components of the bacterial cell wall (licopid, actilone), etc (Katsambas and Lotti 2008; Stevens et al. 2014; Pinegin and Paschenkov 2019).

At present, there are both clinical and experimental data on the use of drugs the immunostimulating effect of which is aimed at activating the cellular, monocyctic-macrophage component of the immune system.

Immunomodulators that are the most suitable and acceptable for the human body are natural immunomodulators. Glucosaminylmuramyldipeptide (GMDP) is a systemic analogue of muramyldipeptide, an active fragment of the cell wall of all known bacteria, which has an immunomodulatory effect. The main effect of GMDP in the human body is aimed at cells from the monocyctic-macrophage lineage. When the drug gets into these cells, it enhances a microbialidal function, formation of reactive oxygen species, activity of lysosomal enzymes, stimulates cytotoxicity of NK cells and T-killers towards infected cells, and stimulates synthesis of INF-γ, IL-1, TNFα and a colony-stimulating factor (CSF) (Pinegin and Paschenkov 2019; Khaitov 2020).

In 1949, H.S. Lawrence found that immunity from one person can be transmitted to another person by injecting a leukocyte extract containing signaling immunostimulative molecules called transfer factors (TF). Available scientific data show that, unlike antibodies, transfer factors are a peptide of 44 amino acids and have a low molecular mass (up to 5000 daltons). They are not species-specific and have universal efficacy regardless of the type of donor and recipient (Lawrence and Borkowsky 1996). TFs are natural immunocorrectors and have a multifaceted effect on the immune system: induce, weaken, or normalize a prolonged immune response by regulating the function of T-suppressors, T-killers and macrophages. TFs are composed of 3 main fractions according to their effect on the immune system. Inductors ensure general readiness of the immune system to resist microbial attacks. An antigen-specific set of antigens and cytokines teaches the immune system to recognize various microorganisms in advance. Suppressors do not allow the immune system to affect a defeated infection too long. Also an important aspect of TF is non-specific activation of macrophage reactions that facilitates complete phagocytosis, recognition of any antigens by macrophages and their presentation to other immunocompetent cells (Matz 2001).

Taking the above mentioned into consideration, it is important to study active molecules of transfer factors for their possible use as immunomodulatory drugs in the treatment of pyoderma as they have never been used when treating this pathology.

The goal of the research is to compare the immune status in patients with chronic and complicated pyodermas in the course of a complex pharmacotherapy by immunomodulators based on transfer factors and on glucosaminylmuramyldipeptide.
Materials and methods

The clinical study was multicenter, non-blinded, prospective and randomized. We successively included adult patients over the age of 17 in outpatient and inpatient care due to their severe or chronic forms of streptostaphylo-dermas in Kursk and Orel regional dermatovenerologic clinics. All the patients had indications for immunocorrection as part of a more complex antibacterial therapy.

The criteria for including patients in the study were their consent, recurrent, deep and severe forms of pyoder- mas, absence of systemic and immune-associated diseases.

The criteria for excluding patients from the study were pregnancy, diabetes mellitus, tuberculosis, HIV infection, syphilis, use of medications to treat other diseases, exacer-bated concurrent chronic diseases, resistance of microorganisms to the used antibiotic.

In the course of the comparative study, we examined different immunity parameters of 127 people in real time, out of whom 107 patients had pyodermas (randomly divided at the ratio 1:1 into 3 comparable observation groups) and 20 people were healthy (to gather background data).

Gender, age, clinical and laboratory data were taken into account when forming the groups. Out of 107 patients, 61 (57%) were men and 46 (43%) were women (average age 40.1 ± 15.8 years); 30 people (28%) were diagnosed with furunculosis, 17 (15.9%) – with hydra-genitis, 16 (15%) – with sycosis, 23 (21.5%) – with con-globate acne, 7 (6.5%) – with eczthyma, 11 (10.3%) – with abscesses and contaminated wounds, and 3 (2.8%) – with ulcerative pyoderma.

Treatment regimens, duration, methods of laboratory monitoring of patients were standardized.

All the patients received a conventional antibacterial therapy, which included ceftriaxone (1g. once a day for 10 days) and cycles of vitamin injections (1 ml of 5% solution of thiamine chloride (B1) and 1 ml of 5% solution of pyridoxine hydrochloride (B6) per day for 20 days). Fucorcin was applied topically 2 times a day. When fucorcin dried out, zinc paste and 30% ichthyl ointment were applied.

In addition to the conventional therapy, the patients of the first group were given Transfer FactorClassic by “4Life Research”, USA (Registration No. in Russia: 77.99.11.003.E., certificate of state registration: 004976.03.11 dated 03.03.2011) as an immunotropic agent (2 pills 3 times a day for 10 days). The patients of the second group were given Likopid manufactured by Peptek (Russia) as an immunomodulator containing glucosaminylmuramylidipeptide (GMDP) (10 mg once a day for 10 days). Lipicod, an effective and safe immunomodulator for the treatment of secondary immuno-deficiencies, was chosen due to its specific effect on the immune cells and due to recommendations on its use to treat pyodermas. The patients of the third group (control group) received only a conventional therapy.

The following immunologic parameters were studied in the blood of all the patients and clinically healthy indi-viduals: a) functional activity of human peripheral blood neutrophils, which was measured by spontaneous and stimulated nitroblue tetrazolium reduction test (NBT test); b) phagocytic number (PN); c) phagocytic index (PI) (Nazarenko 1997; Dolgov and Menshikov 2013).

The activity of cellular immunity was measured by the relative and absolute number of T- (CD3) and B- (CD19) lymphocytes, the relative number of T-lymphocytes sub-populations (T-helpers (CD4) and T-suppressors (CD8)) and calculation of the immunoregulatory index (IRI = CD4/CD8), and the number of activated T-lymphocytes HLA-DR (Nazarenko 1997).

The levels of TNFα, IL-4, IL-8, IL-6, IL-10 cytokines were measured by ELISA method, using commercial test kits by Vector-Best LLC.

Statistical methods included the Student’s test (the data were considered reliable at p≤0.05), the Spearman’s rho (P), and quantification (M±m). A statistical analysis of the findings was done using Microsoft Excel XP suite on an Intel Inside I-5 computer.

Results and discussion

Assessment of the parameters that characterize the immune status of patients with pyodermas showed that before the treatment the values characterizing oxygen-dependent antimicrobial systems of phagocytes significantly differed in all the patients from those in healthy individuals (Table 1).

At the same time, there was a statistically significant decrease in the spontaneous NBT-test values (on average from 28.10 ± 1.2 to 24.9 ± 1.2 au) in the patients with pyodermas. The stimulated NBT-test values in patients of all groups also decreased in comparison to the healthy individuals: a) functional activity of human peripheral blood neutrophils, which was measured by spontaneous and stimulated nitroblue tetrazolium reduction test (NBT test); b) phagocytic number (PN); c) phagocytic index (PI) (Nazarenko 1997; Dolgov and Menshikov 2013).

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Table 1. Dynamics of Indicators of Functional Activity of Peripheral Blood Phagocytes in Patients With Pyoderma During Treatment.

| Indicator | Groups | Indicator before treatment | Indicator on the 10th day of treatment | Control group, healthy (n=20) |
|-----------|--------|----------------------------|----------------------------------------|-------------------------------|
| Phagocytic index (PI), % | Group 1 | 61.91 ± 3.9* | 70.91 ± 3.28 | 70.35 ± 3.14 |
| | Group 2 | 60.28 ± 2.57* | 74.68 ± 3.79 | 70.91 ± 3.28 |
| | Group 3 | 59.88 ± 3.96* | 65.03 ± 3.38** | 70.91 ± 3.28 |
| Phagocytic number (PN), c.u. | Group 1 | 3.61 ± 0.13* | 5.58 ± 0.48 | 4.67 ± 0.87 |
| | Group 2 | 3.29 ± 0.48* | 5.57 ± 0.51 | 4.67 ± 0.87 |
| | Group 3 | 3.51 ± 0.14* | 4.21 ± 0.44** | 4.67 ± 0.87 |
| Spontaneous (NBT test), c.u. | Group 1 | 24.71 ± 1.0* | 26.72 ± 1.24 | 29.01 ± 1.85 |
| | Group 2 | 24.93 ± 1.22* | 28.15 ± 1.32 | 29.01 ± 1.85 |
| | Group 3 | 25.1 ± 1.2* | 26.2 ± 1.22** | 29.01 ± 1.85 |
| Stimulated (NBT test), c.u. | Group 1 | 36.0 ± 1.2* | 44.7 ± 1.23 | 49 ± 2.13 |
| | Group 2 | 37.14 ± 1.41* | 50.1 ± 2.11** | 49 ± 2.13 |
| | Group 3 | 35.25 ± 1.26* | 42.3 ± 1.80 | 49 ± 2.13 |
| Neutrophil | Group 1 | 1.62 ± 0.06* | 1.67 ± 0.04 | 1.8 ± 0.06 |
| | Group 2 | 1.65 ± 0.06* | 1.78 ± 0.06** | 1.8 ± 0.06 |
| | Group 3 | 1.63 ± 0.03* | 1.61 ± 0.04 | 1.8 ± 0.06 |

Note: * – (p≤0.05) statistical differences compared to values of healthy individuals; ** – (p≤0.05) statistical differences between groups. The number next to the asterisk indicates the group with respect to which the difference is significant.
An analysis of neutrophil phagocytic activity showed inefficiency of these bactericidal protection mechanisms and revealed that the changes in natural immunity were ipsidirectional in all the patients. Compared to the control group, in the groups of patients we found a decrease in the phagocytic index and phagocytic number of neutrophils by 1.2 and 1.3 times, respectively. This ratio indicated a low neutrophil redox potential and the exhausted functional reserves of these cells.

During the course of complicated pyoderma in none of the 3 groups there was an increased release of oxygen radicals by neutrophil granulocytes (according to the spontaneous NBT test). Their additional activation did not increase their functional activity, which proves inefficiency of oxygen-dependent bactericidal systems and may indicate a disruption in the processes of pathogen destruction.

The immune drugs increased the neutrophil phagocytic number in the first group to 5.58 ± 0.48 and in the second group to 5.57 ± 0.51, which significantly differed from the values in the group receiving only conventional therapy (p<0.05).

The use of licopid facilitated more intensive recovery of the anti-infective immunity: neutrophil phagocytic activity rose to 74.68 ± 3.79% in comparison to the group where the patients had received a conventional antibiotic treatment (p<0.05). The NBT-test values approached the values of the control group (spontaneous NBT – 28.15 ± 1.32; stimulated NBT – 50.1 ± 2.11).

Both drugs had a comparable effect on the restoration of the initially reduced neutrophil stimulation index (licopid - 1.78 ± 0.06; transfer factor - 1.67 ± 0.04). However, the improvement of immunological values in the group that had used transfer factors was less significant than in the group that had used licopid.

It should be noted that before treatment most patients had on average by 1.3–1.5 times fewer lymphocytes (CD25+, HLA-DR+) than the healthy individuals. An imbalance in the ratio of T-lymphocyte populations was accompanied by a low functional activity of T-killers (CD8+ cells) – the main cellular factor of the body’s immune defense. That indicates the development of immunodeficiency in patients with severe forms of pyoderma.

As a result of the treatment (Table 2), the number of CD4+, CD8+, CD19+ lymphocytes completely returned to normal in 86.0 ± 3% of the patients in the group treated with licopid and only in 60.0 ± 4% of the patients in the group where transfer factors had been used in combination with a conventional therapy. At the same time, there was an increase in the expression of cells with markers CD25+, CD95+ and an increase in HLA-DR+ lymphocytes to normal levels in 96.0 ± 3% of the patients in the second group and in 60.0 ± 2% and 55.0 ± 2% of the first and second groups, respectively.

The results of the study show that before the therapy the majority of the patients (102 patients, or 95.3%) with various forms of pyoderma had some disruptions in the cytokine component of the immune system (Table 3). Those disruptions were most pronounced in the produc-

| Table 2. Dynamics of Systemic Immunity Indicators in the Comparison Groups During Treatment |
|-----------------------------------------------|
| **Indicator, %** | **Groups** | **Before treatment** | **After treatment** |
| CD4+ | Group 1 (n=35) | 29.21* | 35.13 ± 1.1 |
| | Group 2 (n=36) | 29.38* | 37.14 ± 1.40** |
| | Group 3 (n=36) | 29.42* | 33.12 ± 1.95 |
| HLA-DR- | Group 1 (n=35) | 22.45* | 23.2 ± 1.1 |
| | Group 2 (n=36) | 22.64* | 26.1 ± 1.84** |
| | Group 3 (n=36) | 21.91* | 23.8 ± 1.2 |
| CD19+ | Group 1 (n=35) | 11.82 ± 0.94* | 12.85 ± 1.3 |
| | Group 2 (n=36) | 11.39 ± 0.97* | 12.95 ± 1.3 |
| | Group 3 (n=36) | 11.8 ± 1.0* | 12.92 ± 1.3 |
| HLA-DR- | Group 1 (n=35) | 9.37 ± 0.56* | 14.12 ± 1.43 |
| | Group 2 (n=36) | 9.41 ± 0.71* | 15.12 ± 0.83 |
| | Group 3 (n=36) | 9.38 ± 0.62* | 14.44 ± 1.65 |
| CD4+CD8+ | Group 1 (n=35) | 0.8* | 1.5 |
| | Group 2 (n=36) | 0.88* | 1.65±0.1 |
| | Group 3 (n=36) | 0.9* | 1.42 |

**Note:** * – (p≤0.05) statistical differences compared to healthy individuals; ** – (p≤0.05) statistical differences between groups. The number next to the asterisk indicates the group with respect to which the difference is significant.

| Table 3. Dynamics of Cytokine Indices in the Comparison Groups During Treatment |
|-----------------------------------------------|
| **Indicator, %** | **Groups** | **Before treatment** | **After treatment** |
| TNF-α | Group 1 (n=35) | 6.21 ± 0.07* | 4.4 ± 0.06 |
| | Group 2 (n=36) | 6.64 ± 0.09* | 2.8 ± 0.06** |
| | Group 3 (n=36) | 5.94 ± 0.09* | 4.3 ± 0.03 |
| IL-6 | Group 1 (n=35) | 27.81 ± 1.08* | 14.82 ± 2.4 |
| | Group 2 (n=36) | 30.03 ± 1.64* | 12.3 ± 2.6 |
| | Group 3 (n=36) | 30.04 ± 1.72* | 16.4 ± 2.31 |
| IL-8 | Group 1 (n=35) | 40.91 ± 3.72* | 19.2 ± 1.54 |
| | Group 2 (n=36) | 41.03 ± 2.15* | 18.36 ± 2.2 |
| | Group 3 (n=36) | 38.12 ± 1.27* | 16.4 ± 2.31** |
| IL-4 | Group 1 (n=35) | 16.53 ± 1.95* | 24.75 ± 1.45 |
| | Group 2 (n=36) | 18.01 ± 1.38* | 28.96 ± 1.54** |
| | Group 3 (n=36) | 17.91 ± 1.45* | 21.48 ± 1.66 |
| IL-10 | Group 1 (n=35) | 19.81 ± 1.23* | 16.2 ± 2.1 |
| | Group 2 (n=36) | 20.84 ± 1.71* | 16.8 ± 1.74 |
| | Group 3 (n=36) | 20.03 ± 1.64* | 14.52 ± 1.3** |
| | Group 3 (n=36) | 12.71 ± 1.1 |

**Note:** * – (p≤0.05) statistical differences compared to healthy individuals; ** – (p≤0.05) statistical differences between groups. The number next to the asterisk indicates the group with respect to which the difference is significant.

The correlation analysis proved a significant direct correlation between the severity of clinical symptoms of all forms of pyoderma and the level of IL-6 (P= 0.76, p<0.01).

The drugs used during the study helped to normalize the ratio of the cytokines under study. In the patients who had received a complex therapy with licopid or transfer...
Licopid demonstrated more significant influence on the cellular component as the number of patients with the normalization of T-cell number in the likopin-treated group was by 26% (p≤0.05) higher than that number in the group treated with transfer factors.

The studies carried out after the course of treatment with immunomodulators revealed a positive effect of immunomodulators on the cytokine component: no significant difference in the clinical groups (except for the levels of TNFα) was found. We can assume that cytokines are involved in the first phase of TF action as transfer factors already contain a set of antigen-specific cytokines with the help of which the immune system can recognize various microorganisms in advance and affect suppressor cells, thereby controlling a degree of the inflammatory process (Vorob’ev et al. 2004).

Two mechanisms are involved in the immune response to a microbial intervention: an adaptive mechanism – with antigen-specific reactions that form cellular memory – through the expression of pattern recognition receptors (PRRs) that interact with molecular structures of antigens (PAMRs) on the surface of effector cells of monocytes, macrophages and NK-cells; and an innate mechanism – with a quick response to antigen load without remembering the pathogen due to TLRs-receptors isolated on the surface of immune cells (monocytic/macrophage component) which are a subtype of PRRs. Stimulation of TLRs receptors with microbial antigens through NF-kB activates the release of such inflammatory mediators as IL-1, IL-6, IL-8, TNF-α, resulting in complete destruction of pathogens by mononuclear and NK-cells (Kim 2005).

Considering this, we may also explain a more pronounced immunostimulating effect of Licopid by the fact that it acts through the components of innate immunity as well. What confirms this is that glucosaminylmuramylidipeptide being a part of the drug is an equivalent of muramylidipeptide – an active fragment of a bacterial cell wall. The literature describes the cellular-cytosolic NOD2-receptor of innate immunity which the derivatives of muramylidipeptide, glucosaminylmuramylidipeptide and Likopid bind upon when entering the body (Modlin et al. 2012). It is also confirmed by studies of other similar immunomodulators that have received approval for medical use in Japan (Romurtid) and in the European Union (Mifamurtid) (Pinegin and Paschenkov 2019). All these drugs, being muramylidipeptide derivatives, are recognized by intracellular NOD1 and NOD2 receptors and have the same effect on target cells through the mechanisms of innate immunity (Girardin et al. 2003a; Girardin et al. 2003b; Strobe et al. 2006), thereby activating phagocytic activity.

Our studies have confirmed that Likopid is immunotrophic and has the ability to selectively affect specific components of the immune system (Khaitov 2020), in this particular case, cellular and phagocytic components. Besides, scientific studies have proven that GMDP modulates intracellular signaling pathways of NK-cells, enhances their cytolytic capacity (Gur'yanova et al. 2020; Matalon et al. 2016), which accounts for a more obvious immunotrophic effect of the drug.
Conclusion

The glucosaminylmuramyldipeptide-based drug is more efficient than the drug containing transfer factors; consequently, it can be recommended as a drug of choice for non-specific immunocorrection in the course of a complex pharmacotherapy of pyodermas accompanied by a secondary immunodeficiency.

Conflict of interest

The authors declare no conflict of interest.

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