Clinical feasibility study of an immunotropically active drug for treatment of complicated pyodermas

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Abstract

Introduction: Given a wide range of pathogenesis of the inflammatory process in pyoderma, which involves a variety of links in the immune response, work is underway to find ways to optimize immunocorrection in this pathology. The aim of the study was to evaluate the clinical and economic effectiveness of immunocorrection in severe and chronic forms of pyoderma with drugs from different pharmacological groups.

Materials and methods: The data sources were prospective randomized comparative studies of therapy of 107 pyoderma patients aged 18 to 60 years, divided into groups. The patients of the first group additionally used a biologically active additive containing immunoactive molecules and transfer factors (TF) as an immunomodulator; the patients of the second group used glucosaminylmuramildipeptide (GMDP). The clinical effectiveness of regression of inflammatory symptoms on day 10 of treatment was analyzed. Based on the obtained data, the following types of pharmacoeconomic analysis were performed: calculation of the course price, the cost/effectiveness ratio, and the availability coefficient.

Results and discussion: The results of the study showed that the number of cured patients was 91.4% in the first group and 97.2% in the second group of patients. The treatment cost when using the drug is by 970 rubles smaller; the cost/effectiveness ratio (CER) per patient was 1.8 higher for a drug containing transfer factors and amounted to 25.9. The calculation of the availability coefficient (AC) revealed a difference in glucosaminylmuramildipeptide which was 2.1 times smaller.

Conclusion: It was found that a drug based on glucosaminylmuramildipeptide is a more effective and cost-effective means of immunocorrection in severe forms of pyoderma. This confirms a faster regression of clinical manifestations of the disease and lower cost/effectiveness ratio and availability coefficient.

Keywords

antimicrobial activity, conditionally pathogenic microorganisms, cyclic aminooindoles, non-cyclic aminooindoles, pyrroloquinolones.
Introduction

Given a wide range of pathogenesis of the inflammatory process in pyoderma, which involves a variety of links in the immune response, work is underway to find ways to optimize immunocorrection in this pathology (Paul and Seder 1994; Kilburn et al. 2010; Liu et al. 2011; Steven et al. 2014).

Currently, there are convincing clinical and experimental data on the use of immunomodulators, the stimulating effect of which is expressed in the activation of the monocyte-macrophage link of the immune system, in particular, glucosaminylmuramyldipeptide (GMDP), which is a systemic analogue of muramyl peptide, an active fragment of the cell wall of bacteria (Karabinskaya et al. 2000; Skripkin et al. 2013). Monocyte-macrophage cells are the main target of GMDP in the body. In these cells, the drug enhances a microbicidal function, generation of ROSs, activity of lysosomal enzymes, stimulates cytoxicity of NK cells, T-killers in relation to infected cells, expression of HLA-DR antigens, and synthesis of γ-interferon, IL-1 and TNF (Khaitov and Pinegin 1996). In this way, GMDP stimulates all forms of body anti-infection protection.

It has been established that immunity from one person can be transferred to another person through the administration of leukocyte extract containing signal immunomodulatory molecules, which were called transfer factors (TF) (Lawrence and Borkowsky 1996). Transfer factors are natural immunocorrectors and have a complex effect on the immune system, regulating the function of cells: T-suppressors, T-killers and macrophages. Also, TF can activate macrophage reactions in a non-specific way, facilitating complete phagocytosis, recognition of any antigens by macrophages and their presentation to other immunocompetent cells (Matz 2001; Vorob’ev et al. 2004). One of the research lines is an attempt to use transfer factors in complex pharmacotherapy, the clinical effectiveness of which has not been studied so far in the treatment of pyoderma.

In addition to full recovery in the treatment of the disease and no need for rehabilitation, the cost of treatment should also be taken into account (Yagudina et al. 2019). Organization of a rational pharmacotherapy is one of the priorities in the applied medicine (Logman et al. 2010). All this necessitates a comparative analysis of the recommended pyoderma treatment schemes, and a local clinical and economic study is one of the methods of obtaining reliable data.

Aim

To substantiate the inclusion of natural immunomodulators, transfer factors and glucosaminylmuramyldipeptide in the complex therapy of severe and chronic pyodermas based on the evaluation of clinical and pharmacoeconomic effectiveness.

Objectives

1) to evaluate the therapeutic efficacy of treatment with immunomodulators of glucosaminylmuramyldipeptide and transfer factors in comparison with the standard antibacterial therapy in patients with pyodermas; 2) to perform a pharmacoeconomic evaluation with determination of the course cost of the studied drugs and the cost/effectiveness ratio; 3) to calculate the availability coefficient for the drugs; 4) to make a comparative analysis of the therapy outcomes.

Materials and methods

A comparative open prospective randomized clinical trial has been conducted in the regional healthcare facilities in two cities of the Russian Federation (Oryol and Kursk). The program of the thesis work was approved at the meeting of the Ethical Committee of Kursk State Medical University (Minutes of meeting № 4 of April 14, 2014) in accordance with the provisions of the Basic Legislation of the Russian Federation “On Public Health”.

There were 107 persons under study, 61 (57.0%) of whom were men, and 46 (43.0%) of whom were women (average age 40.1±15.8 years). Among them, 30 (28.0%) were diagnosed with furunculosis; 17 (6.5%) were diagnosed with sycoctis; 23 (21.5%) were diagnosed with acne conglobata; 7 (6.5%) were diagnosed with eczema; 11 (10.3%) were diagnosed with abscesses and infected wounds; 3 (2.8%) were diagnosed with chronic ulcerative pyoderma. In 78 patients, the process was widespread and chronic with localization on the face, the torso, and the extremities; in 29 patients, there was local acute inflammation of the skin and the soft tissue.

The patients enrolled in the study were randomized at a ratio of 1:1 and divided by blind sampling into three statistically comparable groups. When dividing into groups, the following aspects were taken into account: sex, age of a patient, form of pyoderma, occurrence of the skin process, severity of the disease, degree of microbial contamination, and laboratory findings.

The criteria for inclusion in the study were willingness to participate in the study, a signed informative consent; male and female patients aged 18 to 60 years undergoing in-patient treatment for severe and chronic pyodermas; indications for systemic antimicrobial and immunotropic therapy; no resistance to the antibiotic used.

The exclusion criteria were history of allergic reactions and individual intolerance to the components contained in the studied drugs; pregnancy, concomitant chronic conditions in the acute phase; use of systemic drugs (cytokines/anti-cytokines, retinoids, immunosuppressors) for other diseases.

All the patients received the basic antibacterial therapy according to the Standard of Medical Care for Pyoderma Patients (Ministry of Health of the Russian Federation, 2005). It included: ceftriaxone (1 g once a day for 10 days), alternating injections of vitamins (1 ml of 5% solution for thiamine chloride (B1) injections) and (1 ml of 5% solution of pyridoxine hydrochloride (B6) once a day for 10 days). Fucorcin (2 times a day), zinc oxide ointment and 30% ichthammol ointment were applied topically.
In addition to the standard treatment scheme, the patients of the first (n=35) study group were prescribed a biologically active additive, Transfer Factor<sub>class</sub> by 4Life Research, USA, as an immunotropic drug (RC registration No. 77.99.11.003 E, certificate of registration 004976.03.11 dated 03.03.2011) in a dose of 2 capsules 3 times a day for 10 days (Vorob’ev et al. 2004).

The patients of the second (n=36) study group were prescribed an immunomodulator drug, Licopid (produced by Russian company Peptek, and containing glucosaminylmuramylidipeptide) 10 mg, according to the following scheme: 1 tablet once a day, 30 minutes before meals, for 10 days (Likopid (tablets of 10 mg) (Vidal).

The patients in the third group (n=36) (control group) received only the basic therapy.

The following dermatological criteria were used to evaluate the effectiveness of the treatment: complete absence of all signs of the disease, i.e. clinical recovery; a decrease in the severity of clinical implications by more than 85%, i.e. a significant decrease; 50–85% symptom reduction, i.e. improvement; a decrease in the symptoms from 20 to 50%, i.e. a slight decrease; no improvement – no effect (Adaskevich 2014).

A pharmacoeconomic analysis of the treatment outcomes was conducted with a ten-day time horizon. The nature of the considered direct medical and direct non-medical costs was determined at the stage of selection of a study design, where they were the same for all patient groups, and thereafter did not impact the calculations during the cost-effectiveness analysis.

The cost/effectiveness ratio was calculated using the following formula 1 (Yagudina et al. 2019):

\[
CER = \frac{\text{cost(RUB)}}{\text{Ef} \%}\tag{1}
\]

Where: CER – cost-effectiveness coefficients of the compared treatment methods;
Cost (RUB) – costs associated with this method in monetary terms;
Ef (%) – clinical effectiveness expressed in appropriate units.

The availability coefficient (Ac) was calculated using formula 2 (Kotlyarova et al. 2019):

\[
(Ac) = \left( \frac{Ac_1 + Ac_2 + Ac_3 + Ac_4}{4} \right)
\]

Where: $Ac_1 = \left( \frac{\text{average price of a drug}}{\text{average wage in the region}} \right) \times 100$;
$Ac_2 = \left( \frac{\text{average price of a drug}}{\text{regional subsistence level}} \right) \times 100$;
$Ac_3 = \left( \frac{\text{cost of a treatment course}}{\text{average wage in the region}} \right) \times 100$;
$Ac_4 = \left( \frac{\text{cost of a treatment course}}{\text{regional subsistence level}} \right) \times 100$.

SPSS 6.0 statistical software package was used for statistical analysis. The statistical significance of differences was determined using Student’s t-test and Mann-Whitney U-test.

### Results and discussion

According to the obtained data (Table 1), it can be concluded that both treatment methods with the prescription of immunomodulators showed almost comparable clinical effectiveness in the treatment of skin and soft tissue infections. Clinical recovery by the tenth day was observed in 91.4% of group I patients, and 97.2% of group II patients (p<0.05), while in group III patients, who had received only the standard antibacterial treatment, this percentage was significantly lower and amounted to 66.6% (p=0.001). It is worth mentioning that in the groups that used additional immunomodulators, the therapy was accompanied by faster resolution of the infection: by the 5th treatment day – in 60.0% (21 persons) of group I and 66.7% (24 persons) of group II in comparison with the patients of group III, in total 27.8% (10 patients).

Analyzing the average recovery time of patients (Table 2), we can see that it was also shorter in the groups using immunocorrection. This was especially evident in the patients who were treated with glucosaminylmuramylidipeptide as an immunomodulator; this difference was more statistically significant (p = 0.001).

The analysis of the dynamics of local inflammatory symptoms showed statistically significant earlier resolution of the pain syndrome and local edema with infiltration. In the patients treated with GMDP immunomodulator, compared to the conventional therapy, 4.5 and 7 days for pain (p < 0.05); 6.0 and 9.5 days for local edema (p < 0.05), respectively. Epithelialization of erosive and ulcerative defects occurred on day 8 on average in the patients receiving GMDP; epithelialization following the conventional therapy occurred only on day 12 of treatment.

The analysis of the regression dynamics of local symptoms of skin and soft tissue infection between the patients in the control groups who received additional immunotrophic drugs showed that statistically significant differences were found in erythema resolution (p < 0.05); it occurred on day 8 in the first group, and on day 6 in the second group.
In the pharmaco-economic studies at stage one of the cost analysis, costs per course of treatment of one pyoderma patient in hospital conditions were calculated. We took into account only the costs of drugs used in complex treatment. For this purpose, the price of one package and the unit cost of the prescribed drug were determined at the beginning.

The cost of a ten-day course of treatment with the drugs used in the conventional therapy, including the price of one package, the number of units of the substance in the package, the and the frequency of use, was the same for all three groups of patients (Table 3). Therefore, further studies on the economic feasibility of the schemes used were not taken into account.

Due to the fact that the studied immune drugs have the relevant indications for use, both comparison drugs are original drugs registered in Russia (RLS 2017; Vidal 2018; RU-Transfer factor); therefore, they are comparable.

At the second stage of the cost analysis of the studied comparison drugs, the course costs for treatment of one pyoderma patient were also calculated with determination of the price of one package and the cost per unit of the prescribed drug.

The comparison drugs included in our pharmaco-economic analysis are presented in Table 4. When determining the price of one package of the drugs shown in the table, the average 2018 prices of Licopid were used, calculated based on the data from Katers price-lists portal (Apteka.ru; Katen; Ministry of Health of the Russian Federation 2005).

Since the biologically active additive Transfer Factor® does not participate in public procurement, its cost was calculated based on the price provided by the manufacturer (RU-Transfer factor).

At the next stage of pharmaco-economic studies, the cost of the prescribed active unit of the studied drugs was determined (Table 5).

The cost of the active unit of the prescribed drug, based on the price per package and the number of units in the package, amounted to 140 rubles for Licopid, and 39.5 rubles for a biologically active additive Transfer Factor®.

After determining the cost of the prescribed active unit of each of the compared medicinal drugs, the cost of treatment of one patient was calculated (Table 6).

Calculation of the course price of the immunotrophic comparison drugs included the frequency and the number of units of prescription. In spite of the fact that the cost of

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**Table 1.** Clinical effectiveness of therapy in patients of control groups depending on diagnosis on tenth day of comparison.

| Diagnosis                                | Therapy + TF n = 35 (100%) | Therapy + Licopid n = 36 (100%) | P       | Conventional therapy n = 36 (100%) | P       |
|------------------------------------------|---------------------------|---------------------------------|---------|-----------------------------------|---------|
| Tenth day                                |                           |                                 |         |                                   |         |
| Furunculosis                             | 9 (90)                    | 10 (100)                        | -       | 6 (60)                            | 0.01    |
| Sycosis vulgaris                         | 4 (100)                   | 6 (100)                         | -       | 6 (100)                           | -       |
| Acne conglobata                          | 6 (75.0)                  | 6 (85.7)                        | 0.05    | 5 (62.5)                          | 0.035   |
| Abscesses and infected wounds            | 4 (100)                   | 4 (100)                         | -       | 2 (66.7)                          | 0.12    |
| Ecthyma vulgaris                         | 2 (100)                   | 3 (100)                         | -       | 1 (50)                            | 0.7     |
| Chronic ulcer pyoderma                  | 1 (100)                   | 1 (100)                         | -       | 0 (0)                             | -       |
| Total                                    | 32 (91.4)                 | 35 (97.2)                       | 0.05    | 24 (66.6)                         | -       |

**Note:** the percentage of patients with clinical recovery from the total number of patients in the group is given in brackets; where p<0.05 (statistically significant differences between groups); TF – transfer factors.

**Table 2.** Recovery time of patients in control groups depending on main diagnosis (M ± m).

| Diagnosis                                | Average recovery time (days) |
|------------------------------------------|------------------------------|
| Tenth day                                |                             |
| Furunculosis                             | 7.4 ± 2.7                   |
| Sycosis vulgaris                         | 4.7 ± 1.8                   |
| Acne conglobata                          | 11.8 ± 3.7                  |
| Abscesses and infected wounds            | 7.2 ± 2.1                   |
| Ecthyma vulgaris                         | 9.0 ± 1.0                   |
| Pyoderma gangrenosum and chronic ulcer pyoderma | 10.0                       |
| Average                                  | 7.6 ± 2.4                   |

**Note:** p<0.05 – statistically significant differences between groups; TF – transfer factors.

**Table 3.** Cost of standard course of treatment (direct medical costs).

| Drug          | Form      | Number of units per package | Package price (rubles) | Frequency of use ADD | Course Price (rubles) |
|---------------|-----------|-----------------------------|------------------------|----------------------|-----------------------|
| Ceftriaxone   | Bottle, 1 g | 1 units ind. pack.          | 18                     | 1 time i/m           | 180                   |
| Vit. B1       | 1 ml amp., 5% solution | 10 units              | 20                     | 1 time i/m           | 10                    |
| Vit. B6       | 1 ml amp., 5% solution | 10 units              | 20                     | 1 time i/m           | 10                    |
| Fusocin (topical) | 1 bottle    | 10 ml                     | 25                     | 2 times 0.5 ml       | 25                    |
| Ichthammol ointment (topical)          | 1 bottle    | 25 g                      | 80                     | 2 times 1* g         | 64                    |
| Zinc oxide ointment (topical)          | 1 bottle    | 25 g                      | 35                     | 2 times 1* g         | 28                    |
| Total cost                                          |               |                            |                        |                      | 317                   |

**Note:** * – The amount of ointment required for application to the foci was equal to two finger-tip units; one finger-tip unit weighs 0.5 g (Hebif 2016).
one unit of transfer factor is lower than that of Licopid, due to the fact that one approximate daily dose (ADD) of Transfer factorClassic was 6 units (capsules), and one ADD of licopid was one unit (capsule), the cost of the daily dose of Licopid was considerably lower than that of the biologically active additive Transfer FactorClassic, and accordingly, the course cost was 970 rubles less.

Based on the proven clinical effectiveness of Licopid as an immunomodulator over the biologically active additive, and the analysis of the cost of pharmacotherapy, the cost/effectiveness ratio was calculated by the formula (3):

\[
CER_1 = \frac{2370 \text{rubles}}{91.4\%} > CER_2 = \frac{1400 \text{rubles}}{97.2\%} \tag{3}
\]

where CER1 is for Transfer FactorClassic, and CER2 is for Licopid.

Calculation of the ratio using the incremental analysis approach showed that in the first group of patients, where the transfer factor as used with the course cost of 2,370 rubles and the effectiveness of clinical recovery in 91.4% of the patients, the cost/effectiveness ratio, CER1 = 25.9, which is higher than that in the licopid group with CER2 = 14.4. Preference is given to the drugs with the lowest ratio (Yagudina et al. 2014).

The cost/effectiveness ratio values are shown in Figure 1.

The data presented in Table 7 show that the total availability coefficient of the drug is 2.1 times lower than that of the biologically active additive.

**Conclusion**

The recommendation of drugs should be decided on the basis of criteria of their effectiveness, safety and affordability.

The analysis of treatment outcomes for patients with severe and chronic pyodermas with immunotropic correction by drugs from different pharmacological groups revealed differences in their clinical effectiveness and economic feasibility.

It was proven that addition of immunomodulators to the combined therapy of severe and chronic pyodermas accelerates the onset of stable clinical recovery in comparison with the conventional antimicrobial therapy (the share of cured patients by day 10 is more than 90% versus 66.6% p<0.001, respectively), contributes to a faster subsidence of all local symptoms of inflammation (pain, edema, erythema and purulent exudate), and significant reduction of recovery time by an average of 4 days, which is associated with direct stimulation of the immunobiological strength of the macroorganism (Akhtyamova et al. 2014).

**Note:** ADD – approximate daily dose.

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**Table 4.** Comparison drugs included in pharmacoeconomic analysis.

| INN                                 | Commercial name | Manufacturer          | Form                | Registration certificate | Price per package (rubles) |
|-------------------------------------|-----------------|-----------------------|---------------------|--------------------------|---------------------------|
| Glucosaminyl-muramyl-dipeptide      | Licopid         | Peptek, Russia        | Tablets No.10 (10 mg) | № LP-002737 dd. 02.12.14 | 1.400                      |
| Transfer factor                     | Transfer FactorClassic | 4 Life Research, L.C, USA | Capsules No.90 (200 mg) | No. 97.99.23.3. U.7085. dd. 10.12.04 | 3.560                      |

*Note: INN – International Nonproprietary Names.*

**Table 5.** Calculation of cost of prescribed unit.

| Drug                  | Form                | Number of units per package | Price per package (rubles) | Price per unit (rubles) |
|-----------------------|---------------------|----------------------------|---------------------------|-------------------------|
| Licopid               | Tablets 10 mg       | No. 10                     | 1.400                     | 140                     |
| Transfer FactorClassic | Capsules 200 mg     | No. 90                     | 3.560                     | 39.5                    |

**Table 6.** Cost analysis of studied drugs for one course of treatment.

| Commercial name | Price per unit (rubles) | Frequency of use ADD | Cost of ADD (rubles) | Cost of one course (rubles) |
|-----------------|-------------------------|----------------------|----------------------|----------------------------|
| Licopid         | 140                     | one tablet 1 time a day | 140                  | 1.400                      |
| Transfer FactorClassic | 39.5             | 2 capsules 3 times a day | 237                  | 2.370                      |

**Table 7.** Availability coefficient for immune drugs compared.

| Commercial name | AC₁ | AC₂ | AC₃ | AC₄ | Total (AC) |
|-----------------|-----|-----|-----|-----|------------|
| Licopid Tablets No. 10 (10 mg) | 5.0 | 15.1 | 5.0 | 15.1 | 10.1 |
| Transfer FactorClassic Capsules No. 90 (200 mg) | 12.7 | 38.3 | 8.5 | 25.5 | 21.3 |

*Note: AC – availability coefficient.*

**Figure 1.** Cost/effectiveness ratio values in the comparison drugs.
Calculation of the cost/effectiveness ratio (CER) also proved the advantage of Licopid, for which it was 14.4 with full clinical recovery of 97.2% of patients, whereas for Transfer FactorClassic it was 25.9 with full clinical recovery of 91.4% of patients.

In addition, the identified difference in the availability coefficient (AC), which is 2.1 times less in Licopid than in Transfer FactorClassic once again confirms the advantages of the drug over the biologically active additive. The lower the ratio, the greater the availability (Kotlyarova et al. 2019).

Due to good clinical effectiveness and economic feasibility, Licopid can be recommended as a starting drug for the nonspecific immunocorrection in the complex therapy of pyoderma in adult patients, and biologically active additive Transfer FactorClassic can be used only as an alternative method.

**Conflict of interest**

The authors declare no conflict of interests.

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