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CYTOKINE STATUS IN PATIENTS WITH ONYCHOMYCOSIS

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Abstract
The study included 42 patients with various forms (distal and proximal) of onychomycosis, in whom the cytokine status was studied during the use of antimycotic and immunomodulatory agents. The studies carried out have confirmed the feasibility of using these drugs in patients with onychomycosis.
Keywords: onychomycosis, cytokine status, treatment.

抽象的
该研究包括 42 名患有各种形式（远端和近端）甲真菌病的患者，他们在使用抗真菌剂和免疫调节剂期间研究了细胞因子状态。 进行的研究证实了在甲真菌病患者中使用这些药物的可行性。
关键词：灰指甲，细胞因子状态，治疗。

Introduction

Onychomycosis is one of the most common fungal diseases in humans. The problem of adequate therapy for onychomycosis is quite significant, given their widespread prevalence among the population, amounting to 2-5% [3,6,7,10,11]. This disease leads to the destruction of the nail plate, creates unpleasant sensations, sometimes accompanied by pain symptoms, which causes anxiety, reduces the efficiency and quality of life of the patients themselves [7,8,9,11].

The most common etiological factor of onychomycosis is Trychophyton rubrum, then Trychophyton mentagrophytes and other dermatophytes, which account for 70-80%

Received: April 12, 2021 / Revised: May 11, 2021 / Accepted: June 13, 2021 / Published: July 23, 2021
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[3,6,11,13]. In recent years, the proportion of other pathogenic fungi (molds, yeasts and their combinations) has significantly increased, which requires a certain correction in terms of the use of certain antifungal drugs [3,13].

The spread of mycotic infection is facilitated by the transmission of the pathogen in swimming pools, saunas, wearing airtight and tight shoes, active use of antibiotics, cytostatics, corticosteroids, contraceptives, as well as concomitant diseases such as diabetes mellitus, obesity, atherosclerosis, peripheral circulation disorders, immunodeficiency states [2 , 7,8,12].

The pathogenetic mechanisms of onychomycosis are very diverse: metabolic disorders in the nail plates are revealed, vascular tone decreases and microcirculatory changes develop, which leads to neurotrophic changes in the nail bed, and a bacterial infection can also join [1,4,8,11].

It should be noted that chronic inflammation develops in onychomycosis, which, on the one hand, proceeds as a self-sustaining exudative-destructive process, and on the other hand, in the form of mononuclear infiltration, which often takes on the character of granulomatous inflammation [7,13]. The variety of variants of granulomatous inflammation, depending on the variety of etiological factors, creates difficulties in the study of the pathogenetic mechanisms of the development of this pathological process [3,8,13]. There are few ways to solve the problem of granulomatous inflammation induced by fungal antigens, although there is evidence of a significant increase in the incidence associated with fungal invasion in AIDS patients, organ transplantation during chemotherapy, after surgery, as well as in young and old people [15] ...

Experience shows that treatment for onychomycosis should be complex and include etiotropic drugs (antimycotics) and pathogenetic agents that are able to correct background disorders (vasoprotectors, immunomodulators, hepatoprotectors, etc.).

The aim of this study was to study the cytokine status in patients with various forms of onychomycosis.

Materials And Methods

In order to study the features of the clinical course and the cytokine status of patients with onychomycosis, as well as to assess the effectiveness of the proposed treatment methods, taking into account the cytokine profile, compared with traditional treatment regimens, an open, randomized, prospective study was conducted. 42 patients with distal and proximal forms of onychomycosis were under observation. We formed the following groups of patients, randomized by sex, age and form of onychomycosis: Ia (14) - patients with distal form of onychomycosis who received pulse therapy with teknazole; Ib (12) - patients with distal form of onychomycosis who received pulse therapy with teknazole in combination with polyoxidonium; IIa (8) - patients with the proximal form of onychomycosis who received pulse therapy with teknazole; IIb (8) - patients with the proximal form of onychomycosis who received pulse therapy with teknazole in combination with polyoxidonium; Group III (22 practically healthy persons).

Of the systemic antimycotics, itraconazole (Teknazole) was chosen, which is the most effective and has a wide spectrum of action in carrying out etiotropic therapy of mycoses. Itraconazole is an antifungal drug and belongs to the azole class. The drug is available in capsules of 100 mg and it can be used for onychomycosis of dermatophytic, mold and yeast etiology []. Itraconazole has proven itself most well when conducting pulse therapy of onychomycosis

(taking 200mg of the drug 2 times a day for 7 days, followed by a 3-week break). Depending on the KYOTOS index, patients with onychomycosis receive 3-4 pulse therapy with itraconazole. As an immunomodulatory agent, we used the well-known drug "Polyoxidonium" (12mg), which was used for 20 days, in between the use of teknazole.

Results And Discussion

Determination of pro- and anti-inflammatory cytokines in blood serum was performed by ELISA using reagents manufactured by Sorbent-LTD (Russia). Statistical processing of the material was carried out using the Excel-2000 software package using the arithmetic mean error and Student's t test.

The study of certain pro- and anti-inflammatory cytokines will make it possible to assess the immune status and determine the ways of immunomodulatory correction, which should be administered differentially, according to the existing international standards [5, 14].

Table 1 presents data on the dynamics of the concentration of interleukin-2 (IL-2) in the blood serum in patients with various forms of onychomycosis.

Table 1. Concentration of IL-2 (pg / ml) in blood serum in patients with onychomycosis during treatment

Examination period	Distal form	Proximal form
Control group	2,3±0,13	2,3±0,13
Before treatment	0,72±0,01º 0,85±0,01º	0,53±0,02º 0,59±0,01º
After 3 months of treatment	1,65±0,01 1,79±0,01	1,39±0,03 0,88±0,01º
3 months after treatment	2,75±0,03 3,77±0,02	3,44±0,05 4,35±0,03º

Note: º - reliability of differences in comparison with the control group at $p < 0.05$.

As can be seen from the data presented, the initial content of IL-2 in the blood serum of patients with onychomycosis was of the same type and significantly reduced in comparison with the data of the control group. After the treatment, in all patients, regardless of the type of therapy, the content of IL-2 increased and in some groups reached the value of the control group, with the exception of patients in group IIb, in whom the level of this cytokine remained almost 2 times lower than the values of the control group.

In 3 months after treatment in patients of group I, regardless of the type of therapy, the concentration of IL-2 in the blood did not differ from the data in the control group. In patients with total dystrophic form of onychomycosis (group II) against the background of antimycotic therapy, an increase in the IL-2 content was noted, which corresponded to the standard value (3.44 ± 0.05, pg / ml and 2.3 ± 0.13 pg / ml at $p > 0.05$ and was significantly higher than the initial level: 3.44 ± 0.05, pg / ml and 0.53 ± 0.02 pg / ml at $p < 0.05$. It should be noted that the additional use of polyoxidonium in patients with onychomycosis this form led to an increase in the concentration of IL-2 by about 7 times.

Table 2 presents data on the dynamics of the concentration of cytokine - tumor necrosis factor alpha (TNF-α) in the blood serum in patients with various forms of onychomycosis. In all forms of onychomycosis, a significant decrease in the concentration of TNF-α was noted, and the most pronounced values were found in the proximal form of onychomycosis. The use of antimycotic drugs led to a noticeable increase in

the concentration of TNF-α in all patients, especially in the group of patients who received an additional immunomodulatory drug polyoxidonium. 3 months after treatment, the TNF-α index approached the values of the control group, although there were noticeable differences in patients with the proximal form of onychomycosis, who were prescribed antimycotic therapy (group IIa) and antimycotic therapy in combination with polyoxidonium (group IIb): 3.67 ± 0, 01pg / ml and 5.12 ± 0.07 pg / ml at p <0.05.

Table 2. Concentration of TNF-α (pg / ml) in blood serum in patients with onychomycosis at different stages of treatment

Observation period	Ia group distal form	IIb group distal form	Ia group proximal form	IIb group proximal form
Control group	4,01±0,31	4,01±0,31	4,01±0,31	4,01±0,31
Before treatment	1,92±0,01º	1,62±0,01º	1,18±0,01º	0,99±0,02º
After 3 months of treatment	2,45±0,03º	3,66±0,04	2,91±0,05º	4,87±0,09
3 months after treatment	3,98±0,05	4,55±0,02	3,67±0,01	5,12±0,07

Note: º - reliability of differences at p <0.05.

In patients with various forms of onychomycosis, another anti-inflammatory cytokine (IL-4) was studied, the results of which are presented in Table 3.

Table 3. Serum interleukin-4 concentration in patients with onychomycosis at different stages of treatment

Observation period	Distal form Ia group	Distal form IIb group	Proximal form Ia group	Proximal form IIb group
Control group	1,9±0,28	1,9±0,28	1,9±0,28	1,9±0,28
Before treatment	5,99±0,05º	5,77±0,05º	7,11±0,15º	7,56±0,17º
After 3 months of treatment	3,95±0,07º	2,93±0,07	4,72±0,18º	3,05±0,17
3 months after treatment	2,11±0,01	2,58±0,01	4,01±0,45º	2,91±0,25

Note: º - reliability of differences at p <0.05.

In all forms of onychomycosis, an increase in the concentration of IL-4 was noted in comparison with the control group, and the changes were more pronounced in the proximal form of mycosis. After treatment, there was a significant decrease in the concentration of IL-4, more pronounced in the group of patients receiving the drug polyoxidonium. The study of the concentration of IL-4 3 months after the end of treatment indicates a tendency for a further decrease in the studied parameter, and the positive dynamics remains to a greater extent in

patients who received complex treatment with antimycotic and immunomodulatory agents.

The available literature contains information on the complex treatment of patients with onychomycosis with antimycotic agents in combination with drugs that improve the trophism of the nail plate, the so-called onychotropic drugs - Onychocid-Emtrix ”[1]. For this purpose, we used a variety of vasoprotective and hepatoprotective agents [4], as well as biotin (vitamin H) [8]. There is information about the immunomodulatory effect in various skin diseases, in particular in psoriasis of the drug polyoxidonium [2], which served as the basis for its appointment in patients with onychomycosis.

Conclusion

Thus, against the background of systemic antimycotic therapy, both Th1 and Th2 pathways of regulation of the immune system are activated. However, the additional inclusion of an immunomodulator in antimycotic therapy led to an earlier normalization of pro-inflammatory cytokines (IL-2 and TNF-α) and a decrease in the content of anti-inflammatory cytokine (IL-4), which may indicate an adequate interaction of the cellular and humoral links of the immune system.

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