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## Investigations of seborrheic dermatitis. Part II. Influence of itraconazole on the clinical condition and the level of selected cytokines in seborrheic dermatitis

Badania nad łojotokowym zapaleniem skóry. Część II.  
Wpływ itraconazolu na stan kliniczny chorych oraz poziom  
wybranych cytokin w łojotokowym zapaleniu skóry

### Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

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### Introduction:

The pathogenesis of seborrheic dermatitis has not been fully elucidated. A number of anamorphic yeasts of *Malassezia* spp. appear to be involved in the intensity of the symptoms. The purpose of the study is to evaluate the levels of selected inflammatory cytokines, IL-2, IL-4, IFN- $\gamma$  and TNF- $\alpha$ , in the serum after treatment with itraconazole.

### Material/Methods:

Sixty-six subjects were enrolled in the study. The control group consisted of 30 participants (23 females and 7 males) without any clinical disorders, aged 24–65 (37.41±6.08 years). Thirty-six patients with seborrheic dermatitis (16 females and 20 males), aged 19–76 (38.61±13.77), constituted the study group. The measurement of IL-2, IL-4, IFN- $\gamma$  and TNF- $\alpha$  levels was performed by ELISA using a Human High Sensitivity kit (Diacclone, France).

### Results:

After six-week treatment with itraconazole administered daily at a dose of 200 mg using pulse therapy, there was remission of the disease or at least substantial clinical improvement in the patients with seborrheic dermatitis. The levels of IL-2 and IFN- $\gamma$  cytokines in the study group were higher than in the control group. After the treatment the level of IFN- $\gamma$  secretion in the male patients with seborrheic dermatitis significantly increased. The levels of the other studied cytokines did not significantly differ.

### Conclusions:

The treatment with itraconazole had a beneficial effect on the clinical condition of the skin of the patients. IFN- $\gamma$  is a cytokine whose secretion might affect the condition of the skin in seborrheic dermatitis.

### Key words:

seborrheic dermatitis • itraconazole • IL-2 • IL-4 • IFN- $\gamma$  • TNF- $\alpha$

## Streszczenie

### Wstęp:

Etiologia łojotokowego zapalenia skóry pozostaje ciągle nie w pełni wyjaśniona. Liczba drożdżaków z rodzaju *Malassezia* może mieć wpływ na stopień zaawansowania procesu chorobowego. Celem pracy była ocena poziomu wybranych cytokin zapalnych IL-2, IL-4, IFN- $\gamma$  i TNF- $\alpha$  w surowicy chorych po leczeniu doustnym itraconazolem.



**Material/Metody:** Badanie przeprowadzono w grupie 66 osób. Grupę odniesienia (O) stanowiło 30 osób (23 kobiety i 7 mężczyzn), klinicznie zdrowych w wieku od 24 do 65 lat ( $37,41 \pm 6,08$  lat). Grupę badaną (B) stanowiło 36 osób (16 kobiet i 20 mężczyzn) chorych na ŁZS, w wieku od 19 do 76 ( $38,61 \pm 13,77$ ). Oznaczeń IL-2, IL-4, IFN- $\gamma$  i TNF- $\alpha$  dokonywano za pomocą zestawu: Human High Sensitivity Elisa (Diacclone, Francja). Klinicznie stopień nasilenia procesu chorobowego oceniano wg skali Scaparro i wsp., w modyfikacji Kaszuby.

**Wyniki:** Po 6 tygodniach leczenia doustnego itrakonazolem podawanym w dawce 200 mg dziennie w terapii pulsowej zaobserwowano znaczną poprawę kliniczną w grupie chorych na łojotokowe zapalenie skóry. Po leczeniu itrakonazolem poziom IFN- $\gamma$  w grupie chorych na łojotokowe zapalenie skóry był istotnie podwyższony. Poziom innych badanych cytokin po leczeniu nie wykazywał znaczących różnic.

**Wnioski:** Leczenie itrakonazolem znacząco wpływa na poprawę stanu skóry chorych. IFN- $\gamma$  jest cytokiną, której wydzielanie może wpływać na nasilenie zmian skórnych w łojotokowym zapaleniu skóry.

**Słowa kluczowe:** itrakonazol • łojotokowe zapalenie skóry • IL-2 • IL-4 • IFN- $\gamma$  • TNF- $\alpha$

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## INTRODUCTION

Anascogenic yeasts from *Malassezia* spp. are members of the commensal microflora of human skin [4, 14]. As some authors have proved, *Malassezia* species are most commonly observed in males, aged about 30, on the skin of a hairy head, upper parts of the trunk and thighs [16]. The most frequently isolated species were *M. sympodialis*, *M. globosa* and *M. restricta* [11]. However, the amount of anascogenic yeasts does not have anything in common with the etiology of seborrheic dermatitis.

The fact that *Malassezia* might be both a commensal and a pathogen leads to a hypothesis that a complicated interaction mechanism between anascogenic yeasts and the human immune system contributes to the etiology of seborrheic dermatitis.

It has been confirmed that when keratinocytes interact with *M. furfur* they release low levels of IL-1 $\beta$ , IL-6, IL-8, and TNF- $\alpha$ . The levels of IL-1 $\beta$ , IL-6, IL-8, MCP-1, and TNF- $\alpha$  remain higher when keratinocytes interact with other species of anascogenic yeasts [18].

The ability of anascogenic yeasts of *Malassezia* spp. to induce and inhibit an immune response has become a focus of scientific studies. When we have understood the mechanism of immunomodulation we might find out why anascogenic yeasts of *Malassezia* spp. are both commensals and pathogens.

Treatment of seborrheic dermatitis should be customized to the needs of an individual patient. The doctor ought to consider the clinical condition, the age, the course of the

disease, the influence of environmental factors and the results of diagnostic tests. The treatment of seborrheic dermatitis should aim at decreasing or eliminating colonies of anascogenic yeasts of *Malassezia* spp. as well as reducing symptoms of inflammation [2].

Numerous studies have confirmed that itraconazole is clinically effective in the treatment of seborrheic dermatitis as it eliminates anascogenic yeasts.

The aim of this study was to compare the concentration of selected inflammatory factors of IL-2, IL-4, IFN- $\gamma$ , and TNF- $\alpha$  in patients' serum before and after treatment with itraconazole.

## MATERIALS AND METHODS

Sixty-six subjects were enrolled in the study. The control group consisted of 30 participants (23 females and 7 males), without any clinical disorders, aged 24–65 ( $37,41 \pm 6,08$  years). Thirty-six patients with seborrheic dermatitis (16 females and 20 males), aged 19–76 ( $38,61 \pm 13,77$ ), constituted the study group. There was no significant difference in age between the groups. We present detailed data on the studied subjects in the tables.

The study involved adult patients with an active disease process. Material for laboratory purposes was isolated exclusively from subjects who, in the period of three months prior to the study, had not undergone any topical or systemic treatment with antimycotic, anti-inflammatory or steroid preparations or had taken part in a blood transfusion. The intensity of the disease process was evaluated on the Scaparro et al. scale, as modified by Kaszuba [8]

Table 1. Characteristics of the groups

Groups	Diagnosis	Sex	Number		Age Min-max	Years X̄	SD
			N	%			
Control group (C)	Clinically healthy subjects	F	23	76.66	25–61	38.19	6.91
		M	7	23.34	24–65	36.16	5.99
		Total	30	100.00	24–65	37.41	6.08
Study group (S)	Seborrheic dermatitis	F	16	44.44	19–76	35.69	13.18
		M	20	55.56	19–48	41.35	14.30
		Total	36		19–76	38.61	13.77
Total			66	100			

Legend: C – control group, S – study group, F – females, M – males.

Table 2. Comparison of the groups – statistical analysis of the results of Table 1

Age – years		Student’s t-test for independent groups	
Compared groups		Test value	Significance of differences
C: F vs M		t=1.19	p>0.05
S: F vs M		t=1.77	p>0.05
C vs S	FM Total	t=1.42 t=1.38 t=1.17	p>0.05 p>0.05 p>0.05

Legend: C – control group, S – study group, F – females, M – males.

**Scaparro scale**

- I. Characteristics of seborrheic dermatitis: erythema, desquamation, itch.
- II. A four-grade scale for evaluation of the intensity of the following symptoms:  
0 – no symptoms, 1 – mild symptoms, 2 – moderate symptoms, 3 – severe symptoms.

The number of affected areas ranged from 1 to 4. The areas were the following: the scalp, face, decollete, and interscapular area.

0 – one area affected, 2 – two areas affected, 3 – three areas affected, 4 – four areas affected.

The total number of points a patient could be given was 13. IL-2, IL-4, TNF-α and IFN-γ were determined in all the patients and healthy subjects.

The blood for cytokine analysis was taken in the morning, on an empty stomach. After complete coagulation of the blood at room temperature, the serum was isolated by centrifugation for 10 min at 1000 × g. The serum was removed and added to Eppendorf tubes. All the serum samples were stored at -75°C in a freezer.

The determination was performed by ELISA using a Human High Sensitivity kit for IL-2, IL-4, IFN-γ and TNF-α (Diaclone, France). The range of sensitivity was from 1.87 to 60 pg/ml. The result was measured with a Pointe 1800 spectrophotometer (Pointe Scientific, Poland) at a wavelength of 450 nm and a wavelength correction of 650 nm. The procedure was performed twice for all the results.

**Statistical analysis**

N – the total number of subjects, n – the partial number of subjects, min-max = range of characteristic variety, x – arithmetic mean, SD – standard deviation, Me – median, % – percentage, t – Student’s t-test, p – significance of differences: < significant difference, > insignificant difference.

The concentrations of interleukin in the control and study groups were compared according to the following pattern: C: F vs M C: F vs S, C vs S: F C vs S: M, C vs S: Total.

Legend: C – control group, S – study group, F – females, M – males.

In the course of treatment of seborrheic dermatitis the researchers administered itraconazole in 100 mg capsules according to the following scheme: one week – 100 mg twice a day and the next week a break from the treatment. Next, on the first and second day of the treatment, 100 mg twice a day; and on the remaining days, a break from the treatment. A similar procedure was applied in the third, fourth, fifth and sixths weeks of the treatment. Student’s t-test was used for statistical purposes.

The Bioethics Committee of the Medical University of Lodz gave its consent to perform this study.

**RESULTS**

Before the treatment the intensity of seborrheic dermatitis according to the Scaparro E. et al. scale was 8.50±3.28 in females and 8.55±2.64 in males; in total for both sexes it was 8.51±3.19 (Fig. 1).



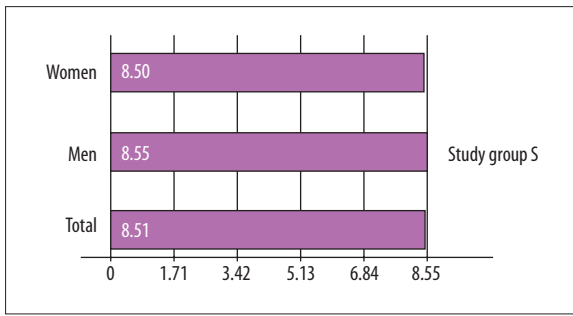


Fig. 1. Mean intensity of skin lesions in the study group with seborrheic dermatitis

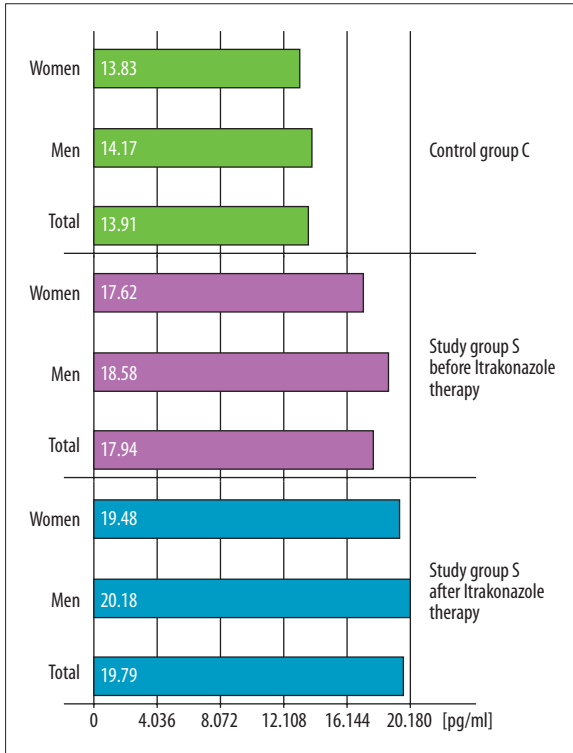


Fig. 2. Mean concentrations of IL-2 in the serum of the study and control group subjects

After the treatment with itraconazole the values significantly decreased and were  $5.37 \pm 3.61$  in females and  $4.95 \pm 3.15$  in males; in total for both sexes it was  $5.18 \pm 3.42$ . The difference was significant ( $p < 0.05$ ).

**Concentration of IL-2 in serum**

Before the treatment the concentration of IL-2 in the patients' serum was  $17.94 \pm 2.88$  pg/ml and was significantly higher in comparison to the control group ( $13.91 \pm 0.96$ ,  $p < 0.05$ ).

After the treatment the concentration of IL-2 increased to  $19.79 \pm 2.88$  pg/ml but the difference was not significant. Sex was not a significant factor (Fig. 2).

**Concentration of IL-4 in serum**

Before the treatment the concentration of IL-4 in the serum of the study group was  $5.27 \pm 1.41$  pg/ml and after the

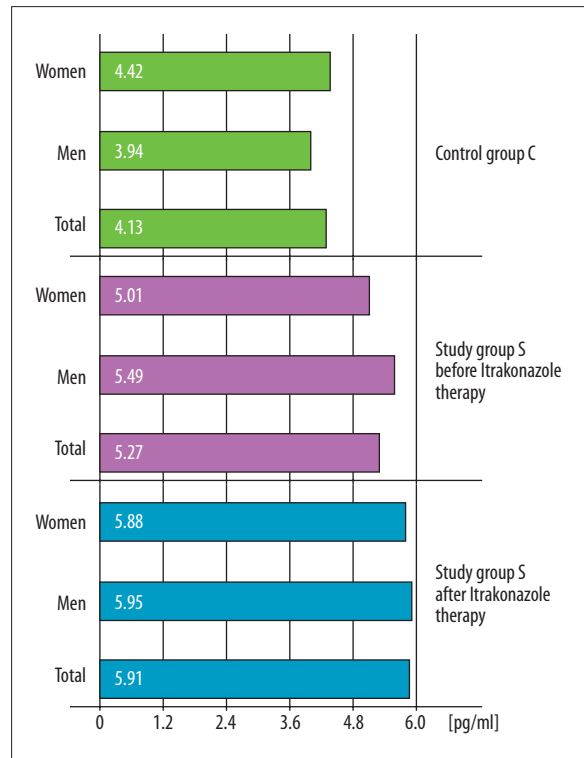


Fig. 3. Mean concentrations of IL-4 in the serum of the study and control group subjects

treatment with itraconazole it was  $5.91 \pm 1.36$  pg/ml. No statistically significant differences between the two groups were observed.

In the female and male groups there were not any statistically significant differences with regard to the concentration of IL-4. The concentration of IL-4 in the control group was  $4.13 \pm 1.41$  pg/ml.

No statistically significant differences between the study and control groups were observed. Nor were there differences between the females and males with regard to the concentration of IL-4 (Fig. 3).

**Concentration of IFN-γ in serum**

The lowest mean concentration of IFN-γ for males and females ( $7.11 \pm 1.41$  pg/ml) was observed in the control group. After the treatment with itraconazole the concentration of IFN-γ in the patients increased from  $10.12 \pm 3.23$  pg/ml to  $12.06 \pm 3.07$  pg/mg. The increase was statistically significant ( $p < 0.05$ ).

We also observed a difference in the concentration of IFN-γ in the serum of the male patients with seborrheic dermatitis after the treatment. Then it was  $13.45 \pm 3.38$  pg/ml. Before the treatment the level was  $9.98 \pm 3.53$  pg/ml. The difference was statistically significant ( $p < 0.05$ ).

**Concentration of TNF in serum**

Before the treatment the mean concentration of TNF in the serum of the patients with seborrheic dermatitis was

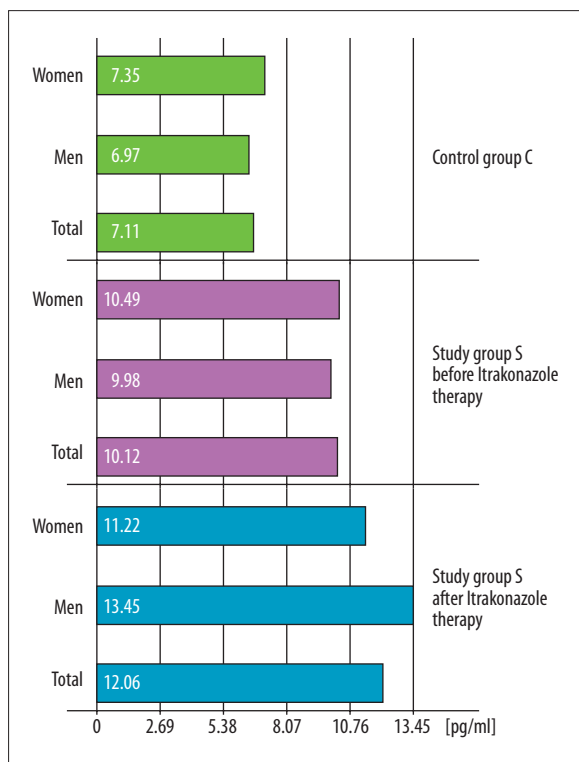


Fig. 4. Mean concentrations of IFN-γ in serum of the study and control group subjects

52.44±9.03 pg/ml. After the treatment it was 59.35±11.16 pg/ml. In the healthy subjects it was 55.11±7.99 pg/ml.

There were no statistically significant differences in the study group before and after the treatment with itraconazole. There were no differences with regard to sex either.

**DISCUSSION**

The etiology of seborrheic dermatitis has not been fully explained yet. Since in the professional literature there is no information on cytokines in seborrheic dermatitis we have decided to discuss other skin disorders in which immune mechanisms play an important role – psoriasis and atopic dermatitis. One of the areas of interest is the problem of inflammatory factors, including pro-inflammatory cytokines, both in the skin and the serum. The reason for determining the concentration of cytokines in the serum is to attempt to discover whether inflammatory diseases of the skin, including seborrheic dermatitis, affect only one organ (in this case the skin) or whether they are systemic diseases.

Based on the current scientific knowledge, we can definitely say that anascogenic yeasts from *Malassezia* spp. contribute to the etiology of seborrheic dermatitis. We can observe an improvement or remission of the disease after the application of itraconazole, which has mycostatic and anti-inflammatory properties [5,9,15]. However, seborrheic dermatitis has recurrent tendencies even after it has been treated with anti-mycotic agents and after a proved decrease in the amount of colonies of anascogenic yeasts on the skin. Thus, researchers are trying to find further solutions.

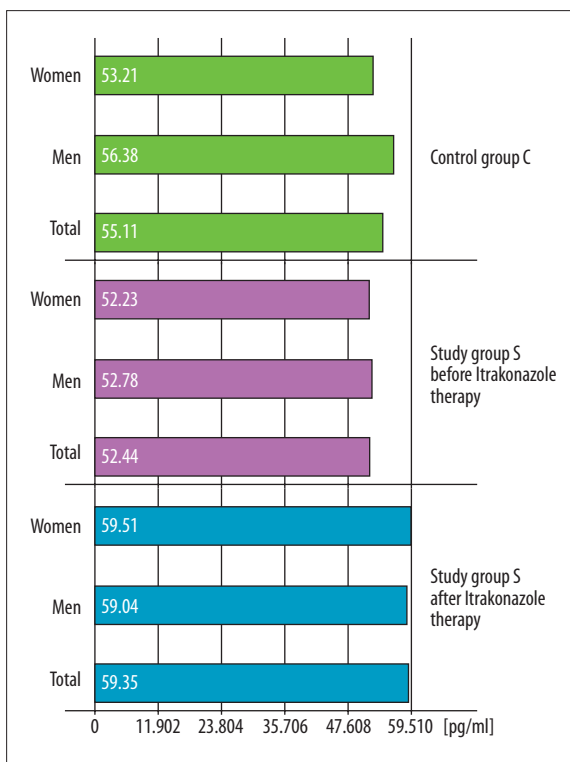


Fig. 5. Mean concentrations of TNF-α in serum of the study and control group subjects

Apart from decreased release of IL-2, we also observed decreased release of cells stimulated by IFN-γ. This observation made them conclude that patients with seborrheic dermatitis demonstrate a decreased cell response to *P. ovale* antigen [12].

In our own studies, we measured the concentration of IL-2 in the serum of patients with seborrheic dermatitis before treatment and 6 weeks after therapy with itraconazole.

Having measured the mean concentration of IL-2 between the group of patients before treatment and the control group, we observed an increase in the level of IL-2, which, however, was not statistically significant.

After the therapy the concentration of IL-2 slightly increased, but the difference remained statistically insignificant (t=-1.16, p>0.05).

**Interleukin 4 (IL-4)**

IL-4 plays various roles in the human immune system. Hamid et al. confirmed that the level of inflammatory infiltrations was high in the acute phase and decreased in the chronic phase [6]. Tazawa obtained different results. He observed low expression of mRNA IL-4 in skin lesions [17]. Similarly, different results with regard to IL-4 concentration were confirmed by Lonati et al. [10].

Professional literature does not present any studies on the concentration of IL-4 in the serum of patients with seborrheic dermatitis or studies on the changeability of the concentration in the studied dermatosis.



Our studies did not confirm that there is a statistically significant difference with regard to the mean concentration of IL-4 in the serum of the analyzed groups.

### Interferon gamma (IFN- $\gamma$ )

Kanda et al. compared the release of IFN- $\gamma$  in response to the fungi *Malassezia furfur*, *Candida albicans* and *Trichophyton rubrum* in patients with psoriasis and atopic dermatitis and in subjects from the control group. They confirmed that in most of the patients with psoriasis, the release of IFN- $\gamma$  was stimulated by applied *M. furfur*. This process was not observed in the patients with atopic dermatitis or in the control group. In a few patients with atopic dermatitis and psoriasis the release of IFN- $\gamma$  was observed after the application of *T. rubrum*. However, with regard to the application of *C. albicans*, the release of IFN- $\gamma$  was observed in all the groups but for atopic dermatitis the release of IFN- $\gamma$  was less intense than in the remaining groups. The release of IFN- $\gamma$ , as a response to *T. rubrum*, was common in the patients with atopic dermatitis, psoriasis and in the control group. All these three groups responded similarly, which means that a low IFN- $\gamma$  release in response to *C. albicans* in the patients with atopic dermatitis is not caused by a general disorder in the release of the factor [7].

Arıcan et al. measured the level of IFN- $\gamma$  with the ELISA method in the serum of patients with psoriasis and in a control group. According to the findings, the level of IFN- $\gamma$  was significantly higher in the serum of patients with psoriasis ( $0.95 \pm 0.907$  pg/ml) in comparison to the control group ( $0.42 \pm 0.465$  pg/ml). The authors used the PASI scale to evaluate the severity of the disease. They confirmed that the concentration of IFN- $\gamma$  is related to the severity of clinical symptoms of the disease. The authors observed an increased level of IFN- $\gamma$  in the serum of patients with psoriasis as well as increased levels of other cytokines (TNF- $\alpha$ , IL-6, IL-8, IL-12, IL-17, IL-18). They might have decided to classify psoriasis as a systemic disease. They also concluded that measuring the concentration of pro-inflammatory cytokines, including IFN- $\gamma$ , might be a method of monitoring patients with psoriasis and may facilitate evaluation of the effectiveness of new therapeutic strategies. The authors proposed a hypothesis that the evaluation of cytokine concentration might be helpful in diagnostics of inflammatory diseases of the skin, such as seborrheic dermatitis and psoriasis [1].

Neuber et al. analyzed the influence of *P. ovale* on monocytes of peripheral blood in patients with seborrheic dermatitis and healthy subjects. *P. ovale* antigens in healthy people definitely stimulated monocytes in the process of releasing IFN- $\gamma$ . This was not observed in patients with seborrheic dermatitis. This observation led them to conclude that patients with seborrheic dermatitis demonstrate a decreased response to *P. ovale* antigens [12].

We observed a significant difference in IFN- $\gamma$  concentration between the study and control groups before the treatment

( $t = -3.27$ ,  $p < 0.05$ ) as well as between the study and control groups after the treatment ( $t = -3.41$ ,  $p < 0.05$ ). A difference in the mean IFN- $\gamma$  concentration in the serum of the male patients before and after the treatment was observed. The difference was statistically significant. Before the treatment the mean IFN- $\gamma$  concentration was 9.98 pg/ml, and after the treatment it was 13.45 pg/ml. The difference might be connected with the fact that seborrheic dermatitis has a more intense and chronic course in males than in females.

### TNF- $\alpha$

Tumor necrosis factor alpha (TNF- $\alpha$ ) is a mediator of the inflammatory response, both systemic and local.

Faergemann et al. analyzed inflammatory cells in the skin in the course of seborrheic dermatitis and also inflammatory factors released by them. They proved that in the skin of patients there are more lymphocytes, macrophages, monocytes, Langerhans cells and granulocytes, both in places free from skin lesions and in places affected by the disease. They compared the patients with subjects with healthy skin. An increased number of intercellular inflammatory factors such as IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$ , IFN- $\gamma$ , IL-12 and IL-14 in the patients with seborrheic dermatitis was observed [3].

Nomura et al. analyzed cytokines in the course of psoriasis and atopic dermatitis. It turned out that in comparison to atopic dermatitis, in skin biotops the expression of TNF- $\alpha$ , IFN- $\gamma$  and IL-1 $\beta$  was reduced. However, the difference was statistically insignificant [13].

Arıcan et al. analyzed the level of TNF- $\alpha$  in the serum of patients with psoriasis and a control group. The concentration of this pan-cytokine in the serum of patients with psoriasis was significantly different ( $25.7 \pm 10.63$  pg/ml) in comparison to the control group ( $11.2 \pm 7.31$  pg/ml). The authors did not observe a relationship between the TNF- $\alpha$  concentration in the serum of the patients and the intensity of skin lesions evaluated on the PASI scale [1].

Our studies included the evaluation of TNF- $\alpha$  concentration in the serum of healthy volunteers who made up the control group as well as in patients with seborrheic dermatitis before and after the treatment with itraconazole. There were no statistically significant differences with regard to TNF- $\alpha$  concentration between the groups. However, the results allow us to conclude that TNF- $\alpha$  concentration tends to increase despite remission of skin symptoms of seborrheic dermatitis.

Summing up, we can say that the concentration of the studied cytokines in the serum of the patients did not significantly change after the treatment with itraconazole, with the exception of the increase in IFN- $\gamma$  concentration. It was higher in the male than in the female patients. This fact might be connected with a more serious course of seborrheic dermatitis in this group.

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The authors have no potential conflicts of interest to declare.

