NARROW-BAND PHOTOTHERAPY AND SODIUM SALT OF THE SYNTHETIC DIAMIDE GAMMA-D-GLUTAMYL-D TRYPTOPHAN AS A COMBINED METHOD OF PSORIASIS TREATMENT: COMPREHENSIVE AND COMPARATIVE EVALUATION

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Abstract

The paper presents the results of a comparative study of various immunosuppressive treatment methods of medium severity vulgar psoriasis (PASI from 10 to 20). The parameters used were PASI indices, p53 apoptosis marker expression indices, and expression indices of T-regulatory cell marker Foxp3. The study involved 96 patients, from 18 to 60 years old, divided by randomization into three groups. Patients in the 1st group (n = 32) received narrow-band phototherapy according to a 4-day regimen. We used the Waldmann UV-7002K instrument and F79/120W-TL01 lamps generating radiation with a maximum emission at a wavelength of 311 nm. We started with a dose of 0.05–0.1 J/cm^2, subsequently increased by 0.05–0.1 J/cm^2 for each procedure, in the absence of erythema. In total, patients received 12–15 procedures, with a course dose of 4.7–7.65 J/cm^2. In the 2nd group (n = 32), patients were treated with the sodium salt of the synthetic gamma-D-glutamyl-D tryptophan dipeptide. Patients of the 3rd group (n = 32) underwent combination therapy, which included both methods described above. As a result of treatment, the greatest decrease in the PASI index, as well as the level of expression of the marker of Foxp3 T-regulatory cells, was observed among patients who received the combined regimen. The data obtained indicate the high therapeutic efficacy of narrow-band phototherapy in combination with the sodium salt of the synthetic gamma-D glutamyl-D tryptophan synthetic dipeptide. It was also noted that the immunohistochemical marker p53, reflecting the cellular renewal of psoriatic papule keratinocytes, is an informative molecular-cellular indicator of the effectiveness of narrow-band phototherapy.

Keywords: psoriasis vulgaris, narrow-band phototherapy, UVB 311 nm, gamma-D-glutamyl-D sodium tryptophan, marker of apoptosis, p53, Foxp3+ T-regulatory cells.

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УЗКОПОЛОСНАЯ ФОТОТЕРАПИЯ И ПРЕПАРАТ НАТРИЕВОЙ СОЛИ СИНТЕТИЧЕСКОГО ДИПЕПТИДА ГАММА-D-ГЛУТАМИЛ-D-ТРИПТОФАНА В КАЧЕСТВЕ КОМБИНИРОВАННОГО МЕТОДА ЛЕЧЕНИЯ ПСОРИАЗА: КОМПЛЕКСНАЯ И СРАВНИТЕЛЬНАЯ ОЦЕНКА

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Резюме

В работе представлены результаты сравнительного исследования различных иммуносупрессивных методов лечения вульгарного псориаза среднетяжёлой степени (PASI от 10 до 20). В качестве оцениваемых параметров использовали индекс PASI, уровни экспрессии

маркера апоптоза p53 и экспрессии маркера Т-регуляторных клеток Foxp3. В исследование были включены 96 пациентов в возрасте от 18 до 60 лет, разделённые методом рандомизации на три группы. Пациенты в 1-й группе (n=32) получали узкополосную фототерапию по 4-дневной схеме. Использовали прибор «Waldmann UV-7002K» и лампы F79/120W-TL01, генерирующие излучение с максимальной эмиссией на длине волны 311 нм. Начинали с дозы 0,05 – 0,1 Дж/см^2, повышая в последующем на 0,05 – 0,1 Дж/см^2 каждую процедуру, при отсутствии эритемы. Всего пациенты получали от 12 до 15 процедур с курсовой дозой облучения 4,7 –7,65 Дж/см^2. Во 2-й группе (n=32) пациентам проводили терапию натриевой солью синтетического дипептида гамма-D-глутамил-D-триптофана. Пациентам 3-й группы (n=32) проводили комбинированную терапию, включающую в себя сочетание двух вышеописанных методик. В результате лечения наибольшее снижение индекса PASI, а также уровня экспрессии маркера Т-регуляторных клеток Foxp3 наблюдали среди пациентов, получивших комбинированную схему. Полученные данные свидетельствуют о высокой терапевтической эффективности узкополосной фототерапии в комбинации с препаратом натриевой соли синтетического дипептида гамма-D-глутамил-D-триптофана. Также было отмечено, что иммуногистохимический маркер p53, отражающий клеточное обновление кератиноцитов псориатической папулы, является информативным молекулярно-клеточным показателем эффективности узкополосной фототерапии.

Ключевые слова: вульгарный псориаз, узкополосная фототерапия, UVB 311 нм, гамма-D-глутамил-D-триптофан натрия, маркер апоптоза, p53, Foxp3+ Т-регуляторные клетки.

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Introduction

Psoriasis is a chronic, multisystem inflammatory disease which most commonly manifests itself on the skin and in the joints. In addition to the physical aspects of the disease, psoriasis has a strong emotional and psychosocial impact on patients: it leads to stigmatization, poor self-esteem and stress, and affects interpersonal relationships [1].

The onset of the disease is induced and supported by dermal infiltrating lymphocytes with secondary increased keratinocyte proliferation and epidermal hyperplasia [2]. A normal balance between apoptosis and cell proliferation supports homeostasis of the epidermal compartment [3]. Psoriasis is a disease associated with decreased apoptosis activity [4]. More and more evidence has been emerging recently showing that two unique subsets of CD4+ T cells can play a role in the pathogenesis of psoriasis: T-helper cells-17 (Th17) and CD4+ CD25+ regulatory T cells (Treg) [5, 6]. The normal function of T-regulatory cells is aimed at suppressing inflammation and autoimmune reactions. A specific marker of Treg is the transcription factor Foxp3, through which their suppressor activity is implemented [7]. It is suggested that a change in the number or functional imbalance of Treg cells in the blood or tissue may cause a decrease in the regulation and subsequent hyperproliferation of T cells, which are pathogenic for psoriasis (Th17) [8].

Despite the significant impact of the disease on the quality of life, its diagnosis and treatment still involves difficulties [9, 10]. Therefore, a better understanding of the pathogenesis of this disease and the available treatment options is needed to ensure optimal therapy [1].

It is known that the basic means of treating mild and moderate psoriasis are such external remedies as topical corticosteroids and vitamin D3 analogues [11]. However, if local drugs do not cause an adequate response or their administration is not practical due to the extensive affected area of the body surface, a more appropriate treatment is systemic therapy [1].

Phototherapy is the main method for treating moderate to severe psoriasis, especially in the form that does not respond to local treatment. The currently available types of phototherapy are PUVA, broadband UVB, and narrowband UVB (NB-UVB). NB-UVB therapy is often used as a first-line treatment [12]. The effect of this method is due to the fact that ultraviolet light causes DNA damage, resulting in overexpression of p53 and, according to some data, stimulation of apoptosis of keratinocytes and T cells in the epidermis and dermis [13]; it changes the cytokine and T-cell profiles towards the predominance of Th2-link, which suppresses the differentiation of Th1/Th17-link lymphocytes and the synthesis of their cytokines (IL-12, IL-22, TNF, IFN-γ) [14].

Another method of systemic influence on the course of psoriasis is therapy with preparation of sodium salt of gamma-D-glutamyl-D-tryptophan, a synthetic dipeptide [15]. Its advantages include non-toxicity, effectiveness even in low concentrations, as well as a wide range of therapeutic doses. The drug has an immunosuppressive effect aimed at humoral and cellular immunity reaction, and it proportionally reduces the levels of T-helpers and T-suppressors, as well as the number of activation markers on lymphocytes, and suppresses T-cells proliferation.

In this study, our goal was to evaluate the effective-

ness of a combination of narrow-band phototherapy and therapy with gamma-D-glutamyl-D-tryptophan (a synthetic dipeptide) sodium salt based on clinical and immunohistochemical data.

The aim of the study was to draw conclusions about the effectiveness of each of the schemes based on comparative data on the expression of the p53 apoptosis marker and the Foxp3 T-regulatory cell marker in psoriatic plaque biopsies of patients receiving various immunosuppressive treatment regimens.

Materials and methods

As part of a cohort open prospective randomized controlled trial, in accordance with the inclusion and exclusion criteria, 96 patients with an advanced stage of vulgar psoriasis were involved in the study while undergoing inpatient treatment in the Budgetary Health Care Insitution "KKVD" of the Omsk Region. The research protocol was approved by the local Research Ethics Committee of Omsk State Medical University.

The criteria for inclusion in the study included age from 18 years, the presence of voluntary informed consent to participate in the study, the duration of the disease at the time of the study for at least 6 months, and the advanced stage of medium severity vulgar psoriasis, which corresponds to the PASI index from 10 to 20.

The exclusion criteria were the presence of decompensated chronic somatic pathology, complicated forms of psoriasis, previous hospitalization for psoriasis less than six months ago, the development of side effects to the therapy administered, a complicated allergic history, patient non-compliance, alcoholism, drug addiction, simultaneous administration of other medications that may affect the course of the primary disease.

All patients were randomly divided into three study groups. Group 1 patients (n=32) received narrow-band phototherapy on a 4-day schedule performed with Waldmann UV-7002K device and F79/120W-TL01 lamps (manufacturer: Herbert Waldmann GmbH & Co. KG, Germany), generating radiation in the wave range of 310-315 nm with a maximum emission at a wavelength of 311 nm. The initial radiation dose was 0.05-0.1 J/cm^2, followed by an increase of 0.05-0.1 J/cm^2 at each procedure subject to the absence of erythema. During hospitalization, patients received the treatment 12-15 times, achieving a course radiation dose of 4.7–7.65 J/cm^2.

In group 2 (n=32), the patients observed were receiving treatment with gamma-D-glutamyl-D-tryptophan sodium salt (OOO Pharma Bio, Russia, registration certificate PN-000022/02 of 10.08.2009). The treatment regimen consisted of two courses of intramuscular injections of 0.1% solution at a dose of 2.0 ml and 1.0 ml daily for 7 days in the first and second courses, respectively, with a 2-day break between courses.

Patients in group 3 (n=32) received combined therapy that included both methods described above.

In all the study groups, patients were also prescribed Retinol palmitate 55 mg + alpha-tocopherol acetate 100 mg, 1 capsule 3 times a day for 14 days, and a 30% solution of sodium thiosulfate, 10 ml, intravenously for 10 days. Externally, 3% sulfur-salicylic ointment and basic care products were prescribed, for the purpose of moisturizing the skin in the stationary stage of the treatment.

The severity and dynamics of the psoriatic process were assessed with the PASI dermatologic index, which was also used as a tool for evaluating the effectiveness of therapy. PASI was calculated with an application developed for this purpose.

In all the studied patients, biopsies of the affected skin areas were performed before treatment and on day 21 of therapy. Immunohistochemical study of p53 and Foxp3 expression in biopsies was performed at the Department of Pathological Anatomy of Omsk State Medical University.

Biomaterial was collected with a DERMO PUNCH skin biopsy needle with a diameter of 4 mm (manufacturer: STERYLAB s. r. l., Italy). Under local incisional anesthesia with 2% lidocaine solution, a biopsy was performed (within the dermis) of fresh morphoelements at the border with healthy skin before treatment, and residual lesions on day 21 of the therapy.

The resulting skin fragments were fixed in 10% neutral buffered formalin (pH 7.2 – 7.4) for 12 – 24 hours, and were fixed in paraffin. Slices were made from the paraffin blocks perpendicular to the skin surface, longitudinally through all layers, with a thickness of 4-5 microns, and were mounted on slides with poly-L-lysine adhesive coating (OOO Bio-Vitrum, Russia, registration certificate no. P3H 2015/2954 of 14.08.2015). The antigens were unmasked in a citrate buffer (pH 6.0) when boiled in water bath for 1 hour. As primary antibodies, ready-to-use (RTU) rabbit monoclonal antibodies were used (Spring Bioscience, Corp., USA, registration certificate No. ФС3 2010/07436 of 20.06.2010): Fohr3, PCH 101 clone, and P53, SPM 514 clone. To visualize the results of the immunohistochemical reaction, the detection kit REVEAL-Biotin-Free Polyvalent DAB (Spring Bioscience, Corp., USA, registration certificate No. ФС3 2010/07437 of 20.06.2010) was used. 3,3-diaminobenzidine tetrachloride, which is part of the commercial detection kit, was used as a chromogen. Cell nuclei were stained with Mayer's Hematoxylin for a period ranging from 30 seconds to 2 minutes.

The expression index of T-regulatory lymphocytes (nuclear label Foxp3) was calculated by counting the number of positively colored cells among the total number of mononuclears (≥1000 cells) in 10 fields of vision (X400), with the results expressed as a percentage. The apoptosis index was evaluated in a similar way.

Microparticles were viewed and photographed with an Axioskop 40 microscope using the AxioCam 503 color

camera (manufacturer: Carl Zeiss Microscopy GmbH, Germany) and ZEN software package.

Statistical processing of the research results was performed with Statistica V. 6 software package and Microsoft Office Excel 2016. The descriptive statistics of quantitative characteristics are represented by the median and standard deviations (in the Me±σ format), and the minimum and maximum indicators were also used. We used nonparametric methods (the Wilcoxon test to check the differences between two samples of paired measurements, the Kraskel-Wallis method to compare three independent groups), and the Spearman correlation coefficient to study the correlation between two variables measured in metric scales on the same sample (where $r \leq 0.3$ is a weak correlation, $0.3 < r < 0.7$ is a moderate correlation, and $r > 0.7$ is a strong correlation). The results were considered statistically significant at $p < 0.05$.

Results

Group 1 included patients aged 19 to 60 years. The duration of the disease varied from one year to 29 years, the median being 14.0±7.29 years. Individual values of the PASI index before treatment ranged from 10.2 to 20.0, median 16.25, and after a course of narrow-band phototherapy, the index decreased by values from 8.0 to 1.2, the median being 2.25.

The 2nd group included patients aged 18 to 60, with the duration of the disease within the range from one year to 44 years (8.0±14.04 years). The values of the PASI index before treatment ranged from 10.0 to 19.5, median 13.9, whereas after treatment they were from 6.0 to 1.3, median 3.25.

Group 3 included patients aged 18 to 60. The duration of the disease varied from one year to 35 years, with an average value of 6.5±8.89 years. The values of the PASI index before treatment ranged from 10.0 to 20.0, median 15.6, whereas after the latest treatment they were from 6.0 to 1.3, median 3.25.

The values of the PASI index before treatment did not differ significantly between the comparison groups ($H=5.83$; $p=0.55$) (see Table 1). After the completion of treatment, each group demonstrated a significant decrease in the index, but it was most significant in group 3, i. e., in patients who received combined therapy ($H=19.65$; $p=0.000$).

Prior to treatment, p53 protein was detected in 2.31-3.82% of epidermal cells, and no statistically significant differences were found among the three study groups ($H=9.2$; $p=0.1$). Positively expressing cells were located in the basal and suprabasal layers of the epidermis (Fig. 1).

After a course of narrow-band phototherapy that is able to induce apoptosis, the expression of the p53

Таблица 1
Динамика значений индекса PASI, экспрессии p53 и Foxp3 до и на 21 день лечения
Table 1
Dynamics of the PASI index, p53 and Foxp3 expression before and on 21 day of treatment

Показатель Indicator	1-я группа 1st group (n=32)	2-я группа 2nd group (n=32)	3-я группа 3rd group (n=32)	Критерий Краскела-Уоллиса, H Kruskal-Wallis test, H	p
PASI до лечения, M PASI before treatment, M	16,25	13,9	15,6	5,83	0,55
PASI на 21 день лечения, M PASI on 21 day of treatment, M	2,25	3,25	1,75	19,65	0,000
Экспрессия p53 до лечения, M p53 expression before treatment, M	2,31	3,82	3,14	9,2	0,1
Экспрессия p53 на 21 день лечения, M p53 expression on 21 day of treatment, M	5,32	1,85	4,86	18,89	0,000
Экспрессия Foxp3 до лечения, M Foxp3 expression before treatment, M	12,1	11,86	11,8	0,47	0,79
Экспрессия Foxp3 на 21 день лечения, M Foxp3 expression on 21 day of treatment, M	5,33	6,5	2,18	36,84	0,000

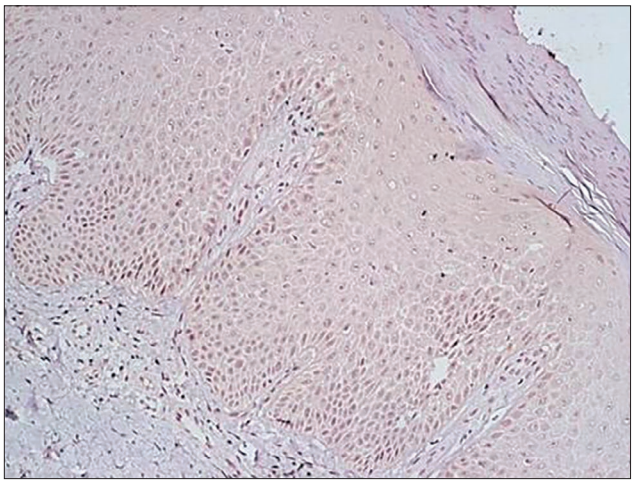

Рис. 1. Позитивно p53-экспрессирующие клетки в псориатической бляшке до начала лечения, Иммуногистохимия. Ув. 200
Fig. 1. Positively p53-expressing cells in psoriatic plaque before treatment, Immunohistochemistry. x200 magnification

marker in group 1 became significantly higher (see Table 2, Fig. 2a), which may indicate the protective function of the protein in relation to skin homeostasis, which is implemented by influencing the glycolysis process and by regulating cell growth. On the contrary, the number of epidermal cells expressing p53 in the skin biopsies of group 2 patients treated with the synthetic dipeptide gamma-D-glutamyl-D-tryptophan sodium salt agent significantly decreased on day 21 of treatment (see Table 2, Fig. 2b), which is consistent with the data of previous studies [15] and indicates the normalization of cellular cooperation and inhibition of hypertrophied functions of cellular immunity. In group 3, an increase in p53 expression was registered in 22 cases, and a decrease was noted in 10. Apparently, based on the research data, it is possible to evaluate the dominant role of a particular therapy method in the regression of the disease in a particular patient. As can be seen from Table 3, an increase in p53 expression was observed mainly in patients who previously received narrow-band phototherapy, while a decrease in the level of expression was observed mainly in those who had previously had only general treatment without immunosuppressive therapy.

Prior to the treatment, the level of positively expressing Foxp3 cells among mononuclear cells of dermal infiltrate ranged from 11.8 to 12.1%. The cells were located in the papillary layer of the dermis (Table 1, Fig. 3a). There were no statistically significant differences among the study groups (N=0.47; p=0.79) (Table 1). At day 21 of the treatment, a significant decrease in the expression of Foxp3-positive cells was observed in each group of patients (T=0.00; p=0.000) (table 2). The most pronounced decrease was in group 3, with the average value corresponding to 2.18% (N=36.84; p=0.000) (Table 1, Fig. 3b).

Таблица 2
Индексы экспрессии p53 и Foxp3+ клеток до начала лечения и на 21 день терапии
Table 2
p53 and Foxp3+ cells expression indices before and on 21 day of therapy

p53	Группы Groups						Foxp3	Группы Groups					
	1-я (n=32) 1st (n=32)		2-я (n=32) 2nd (n=32)		3-я (n=32) 3rd (n=32)			1-я (n=32) 1st (n=32)		2-я (n=32) 2nd (n=32)		3-я (n=32) 3rd (n=32)	
	До Before	21 день 21 day	До Before	21 день 21 day	До Before	21 день 21 day		До Before	21 день 21 day	До Before	21 день 21 day	До Before	21 день 21 day
Медиана Median	2,31	5,32	3,82	1,85	3,14	4,86		12,1	5,33	11,86	6,5	11,8	2,18
Минимум Minimum	0,58	0,87	0,54	0,0	1,11	0,0		10,1	0,3	2,78	0,63	5,78	0,0
Максимум Maximum	8,68	13,75	59,9	45,27	12,43	20,0		15,46	10,77	29,33	25,45	23,3	6,2
Стандартное отклонение Standard deviation	2,1	3,29	10,27	7,81	3,21	4,49		1,43	2,48	6,55	5,3	3,94	1,65
Критерий Уилкоксона, T Wilcoxon test, T	0,00		0,00		167,0			0,00		0,00		0,00	
p	0,000		0,000		0,07			0,000		0,000		0,000	

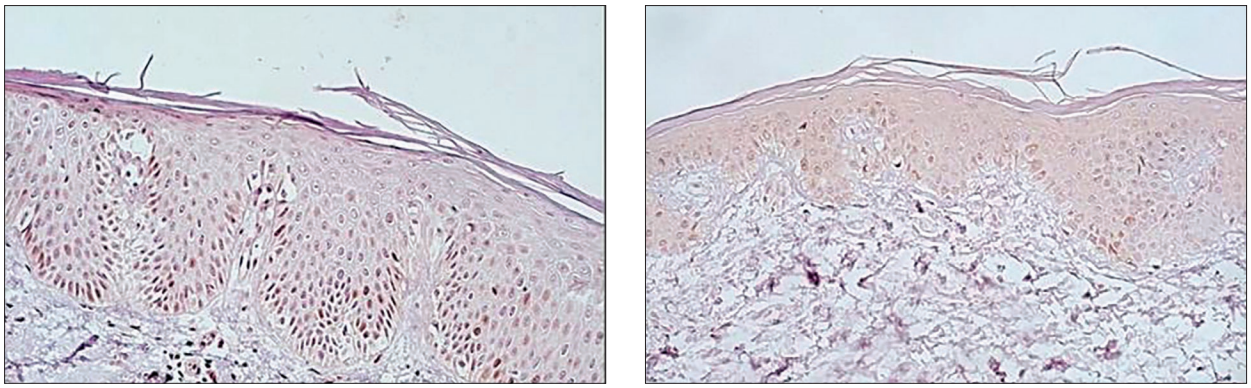

Рис. 2. Позитивно p53-экспрессирующие клетки в псориатической бляшке на 21 день лечения. Иммуногистохимия. Ув. 200
a – 1-я исследовательская группа;
b – 2-я исследовательская группа
Fig. 2. Positively p53-expressing cells in psoriatic plaque on 21 day of treatment. Immunohistochemistry. x200 magnification.
a – 1st research group;
b – 2nd research group

Таблица 3
Изменение экспрессии p53 в биоптатах кожи пациентов, получающих комбинированное лечение, в зависимости от вида терапии в анамнезе
Table 3
Change in p53 expression in skin biopsies of patients receiving combination treatment depending on the type of therapy in anamnesis

Результат комбинированного лечения Result of the combined therapy	Абсолютное число больных Absolute number of patients	Виды лечения в анамнезе Type of therapy in anamnesis			
		Терапия без применения иммуносупрессии Therapy without immunosuppression	Узкополосная фототерапия Narrow-band phototherapy	ПУВА-терапия PUVA-therapy	Метотрексат Methotrexate
Увеличение индекса экспрессии p53,% Increase in p53 expression index,%	22	3	15	2	2
Снижение индекса экспрессии p53,% Decrease in p53 expression index,%	10	8	–	–	2

There were a statistically significant moderate positive correlation and a strong correlation between the PASI index and the levels of Foxp3 + cells: the higher the PASI index in psoriasis, the greater the number of Foxp3+ cells found in the immunohistochemical analysis of the biopsy. There was also a weak negative correlation between the PASI value and p53 expression in group 1: the lower the initial PASI index in patients who received narrow-band phototherapy, the greater the number of p53+ cells detected in immunohistochemical studies (Table 4).

Discussion

This study included a comparative assessment of the dynamics of the PASI index, the expression levels of the p53 apoptosis marker, and the Foxp3 T-regulatory cell marker in patients with moderate psoriasis after treatment with different therapeutic regimens.

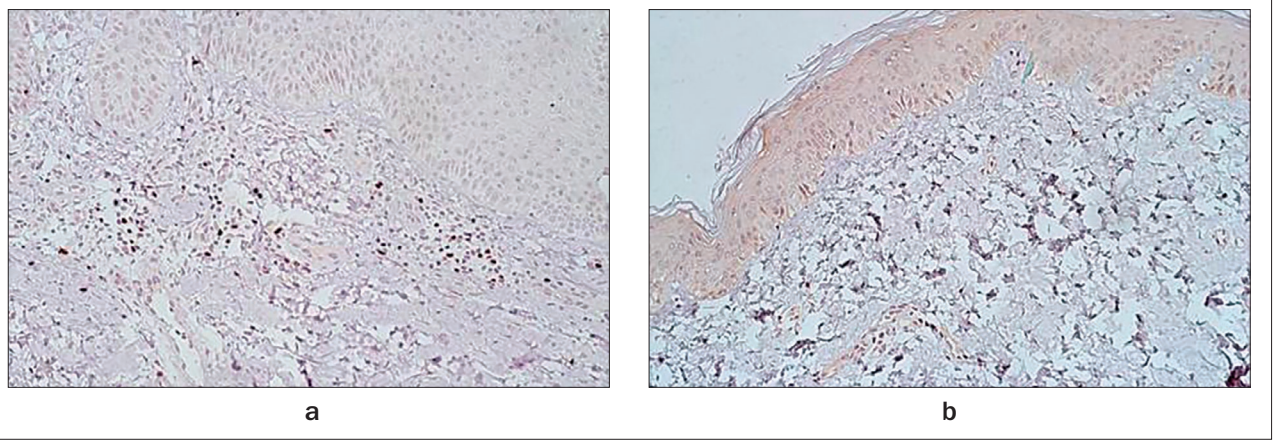

Рис. 3. Foxp3+ клетки в псориатической бляшке. Иммуногистохимия. Ув. 200
a – до лечения;
b – после лечения
Fig. 3. Foxp3+ cells in psoriatic plaque. Immunohistochemistry. x200 magnification
a – before treatment;
b – after treatment

As a result of treatment, the PASI index went down significantly in all study groups, but the greatest decrease was among patients who received combination therapy which included narrow-band phototherapy (UVB 311 nm) and the use of the gamma-D-glutamyl-D-tryptophan sodium salt preparation (group 3).

A study of the level of p53 expression showed a significant increase in group 1, in which patients received only narrow-band phototherapy. In the 2nd group of patients treated with gamma-D-glutamyl-D-tryptophan sodium salt agent, on the contrary, the number of epidermal cells expressing p53 significantly decreased, which indicates the normalization of cellular cooperation phenomena. In group 3, p53 expression levels were different among patients receiving combination therapy. An increase in p53 expression was observed mainly among patients who had previously received narrow – band phototherapy, and a decrease was observed among patients who earlier had been administered only general treatment.

Immunohistochemical staining with Foxp3+ monoclonal antibodies showed that the Foxp3+ cell fraction was significantly reduced in skin biopsies on day 21 of treatment in patients of all the three study groups. The decrease in Foxp3 expression was most pronounced in patients in study group 3.

A positive correlation was found between the PASI index and the level of Foxp3+expression.

Conclusion

As a result of the research, a statistically significant difference in the PASI diagnostic index before and after treatment was found in each study group. However, in

Таблица 4
Корреляция между индексом PASI, экспрессией p53 и Foxp3 в исследуемых группах
Table 4
Correlation between PASI index, p53 and Foxp3 expression within the studied groups

	1-я группа (n=32) 1st group (n=32)		2-я группа (n=32) 2nd group (n=32)		3-я группа (n=32) 3rd group (n=32)	
Показатели Indicators	r	p	r	p	r	p
PASI и Foxp3 PASI and Foxp3	0,81	0,000	0,35	0,000	0,78	0,000
PASI и p53 PASI and p53	–0,3	0,02	0,14	0,26	–0,2	0,12
Foxp3 и p53 Foxp3 and p53	–0,03	0,82	0,09	0,5	–0,08	0,5

group 3, the decrease in the PASI index was significantly more dramatic than in other groups. The obtained data indicate high therapeutic effectiveness of narrow-band phototherapy in combination with the gamma-D-glutamyl-D-tryptophan sodium salt agent. It is interesting that this combination results in a potentiation of the therapeutic effect, but, depending on the previous treatment, one of the methods plays a leading role.

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