PHOTODYNAMIC THERAPY OF PSORIASIS

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Abstract

Photodynamic therapy (PDT) in the treatment of psoriasis remains the subject of much debate. There is no consensus in the scientific community about effective and safe PDT regimens for psoriasis. Described in the published materials doses and concentrations of photosensitizers for psoriasis, as well as light doses, differ by dozens of times. The purpose of this review is to analyze the efficacy and safety profile of various PDT regimens for psoriasis. Some studies demonstrate 100% effectiveness of the method in certain modes (complete or partial clearance of psoriasis foci after PDT). In particular, such efficiency was obtained with the application of 20% 5-ALA (light dose 15 J/cm^2) and 0.1% methylene blue (light dose 15 J/cm^2). The main factor limiting the use of PDT in psoriasis, and in some cases even being the reason for treatment interruption, is severe pain during the irradiation procedure. This requires careful development of PDT regimens in patients with psoriasis.

Key words: photodynamic therapy, psoriasis, 5-aminolevulinic acid, 5-aminolevulinic acid methyl ester.

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ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ БОЛЬНЫХ ПСОРИАЗОМ

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Резюме

Использование фотодинамической терапии (ФДТ) в лечении псориаза остается предметом многочисленных дискуссий. В научном сообществе нет единого мнения об эффективных и безопасных режимах ФДТ при псориазе. Описанные в литературе применяемые для лечения псориаза дозы и концентрации фотосенсибилизаторов, а также световые дозы различаются в десятки раз. Целью настоящего обзора является анализ эффективности и профиля безопасности различных схем применения ФДТ при псориазе. Ряд исследований демонстрирует 100%-ную эффективность метода в определенных режимах (полное или частичное очищение очагов псориаза после проведения ФДТ). В частности, такая эффективность была получена при применении аппликации 20%-ой 5-АЛК (световая доза 15 Дж/см^2) и 0,1%-го метиленового синего (световая доза 15 Дж/см^2). Основным фактором, ограничивающим применение ФДТ при псориазе и в отдельных случаях даже являющимся причиной прерывания лечения, является сильная болезненность во время процедуры облучения. Это требует тщательной отработки режимов ФДТ у пациентов с псориазом.

Ключевые слова: фотодинамическая терапия, псориаз, 5-аминолевулиновая кислота, метиловый эфир 5-аминолевулиновой кислоты.

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Introduction

Psoriasis is a systemic immune-associated disease of a multifactorial nature with a dominant role in the development of genetic factors, characterized by accelerated proliferation of epidermocytes and a violation of their differentiation, immune reactions in the dermis and synovial membranes, an imbalance between pro-inflammatory and anti-inflammatory cytokines, chemokines; frequent pathological changes in the musculoskeletal system [1].

Epidemiology

Psoriasis is one of the most common skin diseases. The disease is equally common in both men and women [2]. Data on the incidence of psoriasis vary significantly in different regions, from 0.14% in East Asia to 5.32% in Central Europe [3].

In general, the incidence is higher in the countries of Eastern Europe and the countries of the Scandinavian Peninsula [4]. A low incidence rate is observed among people in Asia and Africa, in African Americans, Indians, and Japanese [5].

In the Russian Federation in 2020, the prevalence of psoriasis among the entire population was 227.2 per 100 thousand population, and the incidence was 52.5 per 100 thousand population [6]. According to official state statistics in the Russian Federation, the prevalence of psoriasis in 2021 was 243.7 diseases per 100 thousand population, and the incidence was 59.3 per 100 thousand population [1].

Etiology and pathogenesis

The development of psoriasis is primarily associated with genetic predisposition, autoimmune disorders, and environmental factors, including infections and stress [7,8,9]. The pathogenesis of psoriasis is a multifactorial process. One of the factors determining the development of psoriasis is an increase in the expression of pro-inflammatory cytokines. For example, interleukin 17 and interleukin 23 stimulate keratinocyte proliferation and increase the secretion of TNF-α and chemokines that enhance dendritic cell activation, leading to inflammation [9,10,11,12].

Clinical manifestation

Psoriasis is characterized by diverse clinical manifestations from single abundantly scaly papules or pinkish-red plaques to erythroderma, psoriatic arthritis, and generalized or limited pustular psoriasis. Rashes can be located on any part of the skin, but most often, they appear on the extensor surface of the limbs, scalp, and torso. Psoriatic papules vary in size, intensity of the inflammatory reaction, and infiltration that can be very significant and be accompanied by papillomatous and warty growths. In addition to the skin and joints, psoriasis also affects the nail plates [13].

There are three stages in the development of psoriatic rashes [14]: 1) a period of progression or "bloom", when the elements of the rash continue to increase in size, and this usually coincides with the appearance of new rashes and a hyperemic border along their periphery; 2) a stationary period, when the peripheral growth of rashes has stopped, which usually coincides with the cessation of the appearance of fresh rashes; 3) a period of regression, or reverse the development of rashes. It should be noted that the allocation of three stages in the development of psoriatic rashes is only a scheme and there are often deviations from it.

Therapy for psoriasis

Depending on the type of psoriasis, its localization, degree, and severity, various therapy regimens are used for treatment, including topical preparations (based on salicylic acid, vitamin A, tar, etc.), local and systemic use of corticosteroids, calcipotriene, oral systemic preparations (e.g. acitretin, cyclosporine, methotrexate), biologics (etanercept, infliximab, alefacept, efalizumab, and ustekinumab), as well as ultraviolet B (UVB) phototherapy and PUVA therapy [13,15,16].

Studies show high efficacy in the treatment of psoriasis of narrow-band ultraviolet B (NB-UVB, 311 nm) and even excimer laser (308 nm) used as a monochromatic UVB source [17]. These methods are currently used as first-line therapy for stable plaque psoriasis. The first-line therapy for the treatment of refractory psoriatic plaques is PUVA therapy [18].

PDT

Photodynamic therapy (PDT) appears to be an attractive treatment option for psoriasis primarily due to its general and cost-effectiveness [15]. The effectiveness of PDT against various tumor and precancerous skin diseases (including basal cell skin cancer [19], extramammary Paget's cancer [20], and mycosis fungoides [21]) has been proven by numerous studies. At the same time, the use of PDT in the treatment of psoriasis remains the subject of numerous discussions. There is no consensus in the scientific community about effective and safe PDT regimens for psoriasis. In different studies, compounds of different chemical groups are used as photosensitizers in doses and concentrations that differ dozens of times. For example, the effectiveness of the topical application of 5-ALA preparations at concentrations from 0.1% to 20% is described. The range of light dose used is also very wide (from 2 to 37 J/cm^2). The total number of PDT courses and the duration of the intervals between courses also differ.

The purpose of this review is to analyze the efficacy and safety profile of various PDT regimens. A comparison of recent advances in this regard seems to be useful for the further development of the PDT method for the treatment of psoriasis.

Analysis of the published data did not reveal any studies showing a 100% recovery in patients with psoriasis treated with PDT. However, several studies demon-

strate 100% efficiency of the method in certain modes (complete or partial clearance of psoriasis foci after PDT), that is, all psoriasis foci respond (to a greater or lesser extent) to PDT in certain modes. A very important argument in favor of the use of PDT in psoriasis is the fact that several studies have shown that PDT blocks the uncontrolled production of inflammatory cytokines that lead to T-lymphocyte apoptosis and inflammation during the development of psoriasis [22,23]. Even in conditions of incomplete purification of psoriasis foci, a decrease in the intensity of the inflammatory process in them certainly alleviates the condition of patients.

The analysis of the scientific data made it possible to identify 14 studies on the efficacy and safety of PDT with various photosensitizers in patients with psoriasis. Twelve studies assessed the effectiveness of PDT against skin lesions of psoriasis, and two studies assessed the effectiveness of PDT against nail psoriasis. The analysis did not include studies in which PDT was performed in combination with other therapies since the results of such studies do not allow to assess the contribution to the effectiveness of PDT. Comparison of the effectiveness of individual PDT regimens was difficult due to the different assessment methods used in the studies. In part of the studies, the condition of patients was characterized using various indices (NAPSI, SEI, and others), and in the other part, the effectiveness was assessed as complete or partial clearance of lesions.

In most of PDT studies for skin manifestations of psoriasis (9/12), 5-ALA was used as a photosensitizer. In 8 cases it was used in the form of an application, and in 1 case it was given in the form of an oral solution. The concentration of the dosage form of 5-ALA for application varied significantly, from 0.1% (1 study) to 20% (4 studies). The effectiveness of PDT with the application of 5-ALA at a concentration of 20% was higher than for lower doses: up to 100% complete or partial clearance of psoriasis foci using 20% 5-ALA [24] versus only partial improvement in 37.5% of patients after application of 5-ALA at a concentration of 0.1% [25]. At the same time, in a study by Radakovic-Fijan et al. [26] when using 5-ALA at a concentration of 1%, the overall efficiency (completely or partially cleared foci) was 97%, which is very close to the results of PDT for a concentration of 5-ALA 20% (efficiency 100%) [24].

Studies were also analyzed that evaluated the effectiveness of methylene blue (0.1%) [27], hypericin (0.05-0.25%) [28], and 5-ALA methyl ester (ME-ALA) (16%) [29] (one study of each photosensitizer). All of the listed photosensitizers showed high efficiency. Thus, after PDT with methylene blue in 68% of patients with psoriasis, a decrease in the severity of psoriasis by 75% or more was obtained [27].

The only reported adverse events in all studies were pain, itching, and burning during the irradiation session, and in some patients for some time after irradiation. For several patients the study has been discontinued due to severe pain (3/12 patients in the study by Schleyer et al. [25] and 8/29 patients in the study by Radakovic-Fijan et al. [26]). Even though many authors associate the development of pain with the use of high light doses and a high concentration of a photosensitizer, there is no definite certainty in this connection. For example, in a study by Calzavara-Pinton et al. [29], in which the highest light doses of all considered studies (37 J/cm^2) and the highest concentration of 5-ALA (20%) were applied, only 4 out of 17 patients experienced severe pain, and not a single patient came out of studies due to severe pain. It seems more likely that pain sensations may be related to the radiation power density. In both studies, in which some patients had to discontinue treatment, the power density was 60 mW/cm^2. Unfortunately, the radiation power density for PDT was indicated not in all the studies, thus it is not possible to reliably assess the relationship between this indicator and the intensity of pain sensations.

When performing PDT of nails affected by psoriasis, researchers used higher concentrations of photosensitizers or higher light doses. In a study by Shaheen et al. [30] nails were treated with 2% methylene blue solution, in a study by Tehranchinia et al. [31] the light dose was 120 J/cm^2 after application of 5-ALA at a standard concentration of 20%. It should be noted that during irradiation of nails affected by psoriasis, patients did not notice severe pain as it was in PDT of skin foci, even when using a light dose significantly higher than in all other studies (120 J/cm^2). The effectiveness of PDT in both studies was assessed by the NAPSI index, which decreased after PDT by 1.6-2.8 times.

New photosensitizers for PDT in psoriasis

The results of several experimental studies on the evaluation of the efficacy and safety of new photosensitizers in the treatment of psoriasis have been published. Carrenho L.Z.B. et al. [32] report an immunosuppressive effect of a form of porphyrin (5,10-diphenyl-15,20-di(N-methylpyridinium-4-yl)porphyrin) in a mouse model of psoriasis. According to this study, PDT with the specified photosensitizer led to a decrease in the level of pro-inflammatory cytokines, neutrophil infiltration, and proliferation of keratinocytes [32]. In a study by Liu H.Q. et al. [33] the effectiveness of the photosensitizer α-(8-quinolinoxy)phthalocyanine zinc against psoriasis was evaluated. The authors report a decrease in HaCaT cell proliferation and IL-17 mRNA expression after PDT with the indicated photosensitizer. Another group of photosensitizers promising for the treatment of psoriasis are complexes based on NNO-vanadium (IV) tridentate. Lin R.K. et al. [34] demonstrated the anti-inflammatory effects of PDT with these photosensitizers in a mouse model of psoriasis-like skin disease. After PDT, the expression of cytokines IL-17 and IL-22 decreased, which indicates the possibility of alleviating the symptoms of psoriasis.

Таблица
Резюме эффективности фотодинамической терапии у больных псориазом
Table
Summary of the effectiveness of photodynamic therapy in patients with psoriasis

Авторы Authors	Число пациентов* / количество очагов / No. of patients/ No. of lesions	Фотосенсибилизатор Photosensitizer	Режим облучения Light wavelength	Световая доза Light dose	Количество курсов ФДТ Number of PDT courses	Эффективность ФДТ PDT efficiency	Нежелательные реакции Adverse reactions
Boehncke et al., 1994 [35]	3/не указано 3/not specified	10% 5-АЛК, аппликация 5 ч 10% 5-ALA, application 5 h	600-700 нм 600-700 nm	25 Дж/см^2 25 J/cm^2	3 раза в нед 3 times a week	Эффективность ФДТ сопоставима с применением дитранола The effectiveness of PDT is comparable to the use of dithranol	Жжение во время облучения Burning during radiation
Collins et al., 1997 [36]	22/80	20% 5-АЛК, аппликация 4 ч 20% 5-ALA, application 4 h	450-600 нм 450-600 nm	2-16 Дж/см^2 2-16 J/cm^2	12 (3 раза в нед) 12 (3 times a week)	Эффективность (полный или частичный эффект) 25%. Из 80 очагов: 14 – полное очищение; 6 – снижение индекса SEI (ат англ. scale, erythema, and induration – шелушение, эритрема, отвердение) на 30-50%; 60 – незначительное улучшение или отсутствие ответа Efficiency (full or partial effect) – 25%. Of the 80 foci: 14 – complete cleansing; 6 – decrease in the SEI index (at English scale, erythema, and induration – peeling, erythrema, hardening) by 30-50%; 60 – slight improvement or no response	Жжение, покалывание во время и после облучения Burning, tingling during and after irradiation
Robinson et al., 1999 [37]	10/19	20% 5-АЛК, аппликация 4 ч 20% 5-ALA, application 4 h	Широкополосное видимое излучение Broad-band visible radiation	8 Дж/см^2 8 J/cm^2	12 (3 раза в нед) 12 (3 times a week)	Эффективность (полный или частичный эффект) – 74% Из 19 очагов: 4 – полное очищение; 10 – частичный эффект; 5 – отсутствие ответа Efficiency (full or partial effect) – 74% Of the 19 foci: 4 – complete cleansing; 10 – partial effect; 5 – no response	Боль и дискомфорт (80% пациентов во время лечения и 50% между процедурами) Pain and discomfort (80% of patients during treatment and 50% between treatments)
Bissonnette et al., 2002 [38]	12/не указано 12/not specified	Раствор 5-АЛК внутрь 5-15 мг/кг 5-ALA solution orally, 5-15 mg/kg	417 нм 417 nm	1-20 Дж/см^2 Dose, 1-20 J/cm^2	1 раз в нед 1 time per week	Только доза 15 мг/кг показала улучшение состояния пациентов Only the 15 mg/kg dose showed improvement in patients	Легкое жжение при воздействии света Mild burning on exposure to light

Radakovic-Fijan, 2005 [26]	21/63 21/63	1% 5-АЛК, аппликация 4-6 ч 1% 5-ALA, application 4-6 h	600-740 нм 600-740 nm	5; 10; 20 Дж/см^2 5; 10; 20 J/cm^2	2 раза в нед, 6 нед 2 times a week, 6 weeks	Эффективность (полный или частичный эффект) – 97% Из 63 очагов: 8 – полное очищение; 53 – частичный эффект; 2 – отсутствие ответа Efficiency (full or partial effect) – 97% Of the 63 foci: 8 – complete cleansing; 53 – partial effect;w2 – no response	Боль, покалывание, жжение во время облучения и несколько часов после у всех пациентов (8 из исходно включенных в исследование 29 пациентов прекратили лечение в связи с сильными болевыми ощущениями) Pain, tingling, burning sensation during and several hours after exposure in all patients (8 out of 29 patients initially included in the study discontinued treatment due to severe pain)
Fransson et. al., 2005 [39]	8/8 8/8	20% 5-АЛК, аппликация 4-5 ч 20% 5-ALA, application 4-5 h	630 нм 630 nm	10-30 Дж/см^2 10-30 J/cm^2	1 раз в нед, 2-5 нед 1 time per week, 2-5 weeks	Индекс SEI значительно снизился у всех пациентов, с медианы 7 (диапазон 5-9) до 1,5 (диапазон 0-3) The SEI index decreased significantly in all patients, from a median of 7 (range 5-9) to 1.5 (range 0-3)	При дозе света 30 Дж/см^2 многие пациенты испытывали болезненные ощущения, поэтому световая доза была снижена At a light dose of 30 J/cm^2, many patients experienced pain, the light dose was reduced
Schleyer et al., 2006 [25]	9/27 9/27	0,1%, 1% и 5% 5-АЛК, аппликация 0.1%, 1% and 5% of 5-ALA, application	600-740 нм 600-740 nm	20 Дж/см^2 20 J/cm^2	2 раза в нед, 6 нед 2 times a week, 6 weeks	Полного очищение не зарегистрировано. Частичное улучшение: 0,1% 5-АЛК – 37,5%; 1% 5-АЛК – 45,6%; 5% 5-АЛК – 51,2% Complete clearance has not been recorded. Partial improvement: 0.1% 5-ALA – 37.5%; 1% 5-ALA – 45.6%; 5% 5-ALA – 51.2%	Сильные болевые ощущения у всех пациентов (3 из исходно включенных в исследование 12 пациентов прекратили лечение в связи с сильными болевыми ощущениями) Severe pain in all patients (3 out of 12 patients initially included in the study discontinued treatment due to severe pain)
Smits et al., 2006 [40]	8/8 8/8	10% 5-АЛК, аппликация 4 ч 10% 5-ALA, application 4 h	600-750 нм 600-750 nm	2-8 Дж/см^2 2-8 J/cm^2	1 раз в нед, 4 нед 1 time per week, 4 weeks	По 12 бальной шкале исходный индекс степени поражения псориаза в среднем составил 6,6. Через 6 нед в очагах без воздействия фотосенсибилизатора индекс составил 6,2, а для очагов, обработанных ФДТ – 4,2 On a 12-point scale, the initial index of the degree of psoriasis lesions averaged 6.6. After 6 weeks, in the lesions without exposure to the photosensitizer, the index was 6.2, and for the lesions treated with PDT – 4.2	Некоторое жжение и покалывание во время облучения, в целом лечение хорошо переносилось всеми пациентами, и никаких дополнительных анальгетиков не требовалось Some patients experienced some burning and stinging during the irradiation, generally the treatment was well tolerated by all patients and no additional analgesics were needed

Kim et al., 2007 [24]	3/не указано 3/not specified	20% 5-АЛК, аппликация 4 ч 20% 5-ALA, application 4 h	630 нм 630 nm	15 Дж/см^2 15 J/cm^2	1 раз в нед, 7, 10 и 23 нед Once a week, 7, 10 and 23 weeks	Эффективность (полный или частичный эффект) 100%. После лечения во всех случаях наблюдалось незначительное или заметное улучшение Efficiency (full or partial effect) 100%. After treatment, in all cases there was a slight or noticeable improvement	Не сообщалось Not reported
Salah et al., 2009 [27]	16/16 16/16	0,1% метиленовый синий аппликация 0.1% of methylene blue, application	670 нм 670 nm	5 Дж/см^2 5 J/cm^2	Нет данных No data available	Эффективность (полный или частичный эффект) 100% Efficiency 100% (full or partial effect)	Не сообщалось Not reported
Rook et al., 2009 [28]	11/не указано 11/not specified	0,05%, 0,1% и 0,25% гиперицин, аппликация, 24 ч 0.05%, 0.1% and 0.25% of hypericin, application, 24 h	590-650 нм 590-650 nm	8-20 Дж/см^2 8-20 J/cm^2	2 раза в нед, 3 нед 2 times a week, 3 weeks	Наблюдалось улучшение кожных поражений An improvement in skin lesions	Легкое жжение и зуд во время лечения Mild burning and itching during treatment
Calzavara-Pinton et al., 2013 [29]	17/не указано 17/not specified	МЭ-АЛК 16% аппликация 3-4 ч MAL 16% application for 3-4 h	635 нм 635 nm	37 Дж/см^2 37 J/cm^2	В среднем 3,6 (интервал между курсами 9,9±5,6 дней) On average 3.6 courses (interval between courses 9.9±5.6 days)	Из 17 пациентов: у 2 – ухудшение состояния; у 3 – незначительное клиническое улучшение; у 12 – существенное клиническое улучшение. У 5 (28%) косметический эффект оценен, как отличный Of 17 patients: in 2 – deterioration; in 3 – slight clinical improvement; 12 had significant clinical improvement. In 5 (28%), the cosmetic effect was rated as excellent	Боль и жжение в период облучения у 13 (76%) пациентов, в том числе у 4 – слабые, у 4 – умеренные, у 4 – сильные Pain and burning sensation during irradiation in 13 (76%) patients, including 4 mild, 4 moderate, 4 severe
Shaheen et al., 2023 [30]	29/ногти правой руки 29/nails of the right hand	2% метиленовый синий, аппликация 2 ч 2% of methylene blue, application for 2 h	585 нм 585 nm	15 Дж/см^2 15 J/cm^2	1 раз в 2 нед, 6 мес 1 time in 2 weeks, 6 months	Показатели индекса NAPSI для матрицы ногтя снизились в среднем от 7 до 4,5 The NAPSI index for the nail matrix decreased from on average from 7 to 4.5	Небольшие болевые ощущения во время сеанса облучения Slight pain during the radiation session
Tehranchinia et al., 2020 [31]	8/35 ногтей 8/35 nails	20% АЛК, аппликация 3 ч 20% of 5-ALA, application 3 h	630 нм 630 nm	120 Дж/см^2 120 J/cm^2	1 раз в 3 нед, 5 курсов 1 time in 3 weeks, 5 courses	Показатели NAPSI значительно снизились с 5,97±1,29 в начале исследования до 4,29±1,44 на 15-й неделе и 2,11±1,27 в конце 24-й нед наблюдения после завершения ФДТ NAPSI scores significantly decreased from 5.97±1.29 at baseline to 4.29±1.44 at week 15 and 2.11±1.27 at the end of week 24 after completion of PDT	Не сообщалось о сильной боли и дискомфорте во время облучения No severe pain or discomfort was reported during irradiation

*указано число пациентов, завершивших исследование с оцененным эффектом
*the number of patients who completed the study with an estimated effect is indicated

The analyzed data leave no doubt that PDT is an effective and promising treatment for psoriasis. The issue under discussion is the choice of the optimal photosensitizer, its dose (concentration for application), light dose, and irradiation regimen.

Since there is evidence that protoporphyrin IX (PpIX) accumulates with very high selectivity in psoriasis lesions [40], it can be assumed that lower concentrations of 5-ALA than those used for dermato-oncological indications may be sufficient to provide a beneficial clinical effect in psoriasis. This is supported by data from studies in which 5-ALA was used at a low concentration (1%) [26] but with an efficiency close to studies of 20% 5-ALA [27]. In addition, as some authors [40] believe, the main purpose of PDT in psoriasis is probably not a cytotoxic effect, which requires higher light doses, but rather an immunomodulatory effect, which is believed to require repeated exposure to lower photodynamic doses over a longer period.

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