THE TREATMENT OF PSORIASIS – APPROACHES AND ADVANTAGES

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INTRODUCTION
Psoriasis is the most common skin disease of modern times (psoriasis - from the Greek "psora", which means "itchy") affecting 1 to 3 percent of the population (140 to 210 million people are living with psoriasis).⁹ It affects both sexes at any age with higher frequency in areas of limited sunshine (1-2% of the population of the United States, Germany, Russia, Scandinavia and others.) and is less frequent among Mongoloid and Negroid races. The incidence is highest between the ages of 20-39 years for men and 40-59 years for women, with an equal ratio of M-W.²⁶ There is no accurate statistics on the incidence of the disease in Bulgaria. On incomplete data, about 90 000 people, adults and children, suffer from psoriasis in the country. The disease affects the quality of life of patients to an extent comparable to that of other major diseases, such as type 2 diabetes, chronic respiratory diseases, neoplasias.²¹

In psoriasis there is a rapid proliferation of epidermal cells, as the cycle of their growth (regeneration time) is within 7 days, while normal epidermis is on average 28 days (approximately 4 times). Due to this fact epidermal cells do not reach full maturity and abnormal, incomplete keratinization (parakeratosis) occurs. Mitosis in cells is regulated by cyclic adenosine monophosphate, which is significantly reduced in psoriatic epidermis. This violates the arachidonic acid metabolism, which in turn affects the prostaglandins, which are also reduced. A number of immunological processes are established - the presence of antibodies against the stratum corneum and against the nuclei of basal cells, interference in humoral (increasing IgA) and cellular immunity (increase in T lymphocytes, especially in
generalized form), the presence of chemotactic factors (immune complexes and leukotrienes) and the like.\textsuperscript{[28]}

The clinical picture varies depending on the location, nature and size of the rash elements, age and others. There are a variety of clinical variants of psoriasis, which differ in the morphological characteristics of the lesions, in severity and prognosis in relation to treatment. The most common form observed in 80-90\% of patients, is so called plaque-type psoriasis (plaque psoriasis, psoriasis vulgaris), which is characterized by well-limited erythematous squamous plaques located mostly in acres (elbows, knees, capillitium).

An important parameter for assessing the severity of the disease is the percentage of the affected skin area, the so-called Body Surface Area (BSA) index. Cases, in which less than 3\% of the skin surface is affected, are classified as mild psoriasis, between 3 and 10\% - medium severe psoriasis, in cases where over 10\% of the skin surfaces affected are considered severe psoriasis. For an objective assessment of the disease severity also applies the so-called PASI index (Psoriasis Area Severity Index), which in its essence is a comprehensive assessment of the degree of expression of the main symptoms of psoriasis, namely erythema, induration (infiltration) and desquamation in different areas of the body, taking into account the affected area. The highest value of PASI, which meets the most severe form of psoriasis, is "72", and the lowest is "0" and practically corresponds to the lack of psoriatic change. The way the disease affects the quality of life of patients depends on the affected areas, and on many other factors. For example, though limited, lesions on exposed areas of the skin (hands, face, etc.) or in the genital area can be much more traumatic than lesions in other locations. For this reason, assessment of the severity of psoriasis is based on both the BSA, and the quality of life of patients.\textsuperscript{[8, 24]}

**Treatment of the disease**

The treatment is still a problem, as it is not always effective. The range of therapeutic options extends from local therapy, through physiological and phototherapy, climatotherapy and goes as far as systemic therapy and the latest developments in the pharmaceutical industry - biological therapy that targets specific molecules involved in the pathophysiology of psoriasis. The decision of what type of treatment to proceed depends on many factors such as the type of psoriasis, its location, extent and severity of the disease, the patient’s age, gender, quality of life, comorbidities and the various risks associated with treatment.\textsuperscript{[20]}
Local Therapy

Many studies and articles examine local and systemic treatments for psoriasis, their method of administration and risk of side effects.\cite{2, 19, 34, 36}

Particular attention to the attitude of patients to treatment is paid, and shaping recommendations for improving compliance with the local treatment.\cite{6}

They all conclude that local treatment is essentially limited to the use of emollients, keratolytics, corticosteroids, analogs of vitamin D (calcipotriol calcitriol takaltsitol), derivatives of vitamin A (topical retinoid - tazarotene), tars and calcineurin inhibitors (pimecrolimus, tacrolimus) dithranol.

Emollients are an integral part of the local treatment of psoriasis. Emollients (in the form of lotions, creams, ointments and washable products) hydrate the skin, maintain its water-lipid mantle and protect it from various irritants. The efficacy of the independent use of Emollients has been evaluated in several clinical studies, where they are used as control of topical corticosteroids. Their effectiveness varies from 15 to 47%. They are recommended as daily application in the care of the skin of patients with psoriasis, along with other local or systemic treatment.\cite{1, 27}

Keratolytics - Salicylic acid (Acidum salicylicum - C7H6O3) is a local keratolytic tool used for many years in local treatment of psoriasis. It is contained in shampoos, soaps, lotions and gels. The salicylic acid has antiseptic and antibacterial properties. Its derivatives – esters and salts are widely used in medicine. Especially important is the application of acetylsalicylic acid (also known as aspirin) and phenyl salicylate (aka salol). The ability of the salicylic acid to exert keratolytic, bacteriostatic, fungicidal effect and to exfoliate the stratum corneum allows its inclusion in a number of products for topical application in various indications including psoriasis, acne vulgaris, melasma, photodamage, freckles and others. The efficacy and safety (as well as low toxicity) of exfoliation with salicylic acid (peeling products) at different skin types is well documented in the literature.\cite{29, 32}

The exact mechanism of keratolytic action is not fully understood. It is believed that the salicylic acid breaks the bonds between the keratinocytes as well as decreases the pH of the stratum corneum. Its application leads to peeling of the squamae. The risks of application of salicylic acid include systemic toxicity, so it should not be combined with other salicylates.
taken orally. To achieve a keratolytic effect, local preparations containing urea in concentrations of 10-20%. can also be used.

**Ureum (CH\(_4\)N\(_2\)O) – Carbamide** - is an organic compound and represents a derivative of ammonia, known as urea, carbamide, diamide, carbonyldiamide. It is the end product of the metabolic degradation of amino-containing organic compounds. Unlike ammonia, however, urea is not toxic to the body and can be accumulated prior to its separation into urine. The urea used in the cosmetic industry is synthesized artificially from ammonia and carbon dioxide, as it may also be produced in crystalline or liquid form. The concentration of urea included in the composition of the medical cosmetics vary in percentage concentration from 2.0% to 50%.

**Local corticosteroids** - the most commonly prescribed means for the treatment of psoriasis in US and in many other parts of the world.\(^ {18}\) Treatment with local CS is recommended for mild to moderate psoriasis. The application of potent local corticosteroids (CS) - betamethasone dipropionate (C\(_{28}\)H\(_{37}\)FO\(_7\)), leads to a significant improvement or complete clearance of psoriasis lesions in 46-56% of patients. Betamethasone is associated with cytoplasmatic glucocorticosteroi receptors and subsequently translocates rapidly to the nucleus where it stimulates or inhibits the genes regulating inflammation. Steroids affect several symptoms of inflammation (infiltration, erythema, edema and a hyperproliferation), without affecting the ultimate differentiation.\(^ {35}\) To limit the risk of side effects of local CS, the therapy can start with combining them with local analogues of vitamin D3. The combination with other local or systemic agents improves the therapeutic response and reduces the risk of side effects. The choice of the appropriate class of local CS should be tailored to the specific location of psoriatic lesions and patient age (overpowering CS should not be applied to children). They are available in the form of ointment, cream, or foam and scalp shapes in various concentrations.

**Analogues of vitamin D3 for topical application** - provides an alternative to local corticosteroids. Calcipotriol, calcitriol and tacalsitol are among the first vitamin D analogues used for psoriasis. Despite their limited effectiveness and the side effects of local irritation, these agents are not related to skin atrophy.\(^ {23}\)
Analogues of vitamin D3 should be administered with caution in concomitant use with drugs that increase serum calcium levels (for example thiazide diuretics). Simultaneous use of the local Cp and formulations containing salicylic acid can lead to its inactivation.

**Combined preparations with calcipotriol (Calcipotriol combinations)**

In mild to moderate in severity Ps a combination of an analogue of vitamin D3 with local CS or monotherapy with a preparation containing both analog of vitamin D3 and local CS (betamethasone dipropionate) is recommended. Over the past seven years a combination of calcipotriol and betamethasone dipropionate has gained wide acceptance as a useful combination therapy. This has been proven to be more effective than calcipotriol or betamethasone dipropionate alone. It is well tolerated as part of the 4-week cycling with calcipotriol. Recently, the use of calcipotriol and betamethasone dipropionate composition in gel proved to be a useful adjunct in the treatment of psoriasis of the scalp. Randomized, double-blind controlled studies have shown a significant benefit of the combined therapy preparations with one study reporting 92% achievement of control for over 52 weeks.

**Tars (T)**

Tars are classic agents for the treatment of psoriasis. Using tar to treat skin diseases was described almost two thousand years ago by Dioscorides. Tar is a liquid product obtained by the method of dry distillation of solid fuels - coal and charcoal, wood, peat and the like. Tars are resins or modified tar produced from wood and the roots of pine by destructive distillation - pyrolysis. Tar can be obtained from peat. Coal tar is one of the oldest treatments for psoriasis and eczema. It has anti-inflammatory, antibacterial, anti-itching and antimitotic effects. Crude coal tar has been used for the treatment of dermatoses, for many decades. In recent years its use is restricted to skin diseases such as psoriasis and chronic dermatitis.

Short-term side effects are folliculitis, irritation and contact allergy. Coal tar contains the carcinogens. It is not clear evidence of an increased risk of skin tumors or internal tumors. Until now, most studies were relatively small and they do not investigate the risk of coal tar alone, but the risk of coal tar in combination with other therapies. New, well-developed, epidemiological studies are necessary to assess the risk of skin tumors and other malignancies after dermatological use of coal tar. Tar is mainly used for the treatment of chronic plaque psoriasis, scalp psoriasis, atopic dermatitis, seborrheic dermatitis, alone or in combination therapy with other drugs, phototherapy, or both. Professional studies have shown its
carcinogenic character, although epidemiological studies have not confirmed categorically similar results when used locally.\textsuperscript{[13]}

**Pix Juniperi, Juniper tar** - contains phenols (guaiacol, cresol, etilgvayakol, propilengeayakol) homologous compounds of the acetic acid - cadinene. It acts astringently, slightly resorptively, antiseptically, antipruritically. At higher concentrations - revulsively and keratolytically. Juniper tar is a component (either alone or in combination with other active ingredients) of a number of products in the form of ointments, lotions, creams, shampoos in psoriasis, eczemas, neurodermatitis, seborrheic, dermatoses exudative dermatoses, rarely shows irritant effect. Photosensitivity. The activity of the tars is potentiated by sulfur and salicylic acid. It starts with low concentrations (0.5-1%). Glycerin improves tolerability.

T is used in magistral formulations, making it significantly cheaper than other topical agents. It is used in a concentration of 5-20% as an ointment or gel, usually once daily. The use of T for the treatment of P is recommended in cases where, for various reasons, other topical agents can not be applied. It may be administered in combination with UV-B phototherapy. It is not recommended during pregnancy, lactation and children under 7 years of age.

**Topical retinoids**

**Retinoids** are compounds that have properties similar to those of vitamin A. They stimulate the differentiation of cells, inhibit the malignant transformation of the skin. Topical retinoids are hydrogels without color and smell. In prolonged use, they do not cause skin damage. There is no risk involved of deterioration in stopping the treatment, as with corticosteroids. Monotherapy with systemic retinoids has limited effect.

Tazarotene is the first of a new generation of acetylene retinoids developed for the topical treatment of mild to moderate plaque psoriasis.\textsuperscript{[38]} It is recommended that the treatment should start with tazarotene gel 0.05% once daily in the evening for about 1-2 weeks and then switch to tazarotene gel 0.1% for another 1-2 weeks. It is not to be used during pregnancy and lactation. The most common side effects are burning, itching, redness and irritation of the skin, therefore concomitant use of irritating and drying skin products should be avoided. To reduce the common local side effects, tazarotene can be combined with local CS. The application of tazarotene in the evening in combination with local CS in the morning is a recommended regimen for improving the efficiency of local resources and reducing the risk
of their side effect. In Bulgaria, the preparation is not available in the pharmaceutical network.

Systemic therapy
The choice of systemic therapy is based on the doctor's experience, relevant past medical history and patient choice.\[39\]

Methotrexate is a structural analogue and competitive antagonist of the folic acid. It inhibits dihydrofolate reductase which violates turning the dihydrofolic acid into tetrahydrofolic one, involved in the synthesis of DNA and RNA. It is generally considered to be the gold standard in the management of psoriasis – it is well tolerated, effective, and is used in the long term. Mtk is indicated for the treatment of moderate to severe degree of PV. It is also effective in the treatment of psoriatic arthritis.\[7\]

Retinoids have proven to be a useful alternative in the treatment of psoriasis for more than 20 years. They demonstrate efficacy in a selected group with response rates of approximately 40%.\[16\]

Acitretin - the basic composition of the group used to treat psoriasis vulgaris is acitretin. Studies show that acitretin is particularly useful in erythroderma and pustular psoriasis. Studies have shown that retinoids block the action of vascular endothelial growth factor (VEGF) and that VEGF genotype may have a prognostic role in predicting response to acitretin therapy in patients with type 1 chronic plaque psoriasis.\[5, 39\]

The dosage of acitretin is strictly individual and depends on the therapeutic response and tolerability. It is necessary to exercise paraclinical control before and during treatment with strictly monitored blood counts. In therapy lasting for about 1-2 years it is recommended to perform X-ray control of the spine and joints to exclude possible ossification.

Fumaric acid esters have been introduced in the treatment of psoriasis by the German dermatology school while their systemic use has not been studied in our country.\[25\] In Europe and in Germany in particular, fumarate therapy has proven to be a very effective alternative for over 40 years.\[31\] The mechanism of their action is not understood, but scientists suppose that there occur inhibition of keratinocyte proliferation and directing the immune response of Th1-Th2-dominant type. Fumarates are suitable for the treatment of moderately severe PV.\[10\]
Cyclosporin is a powerful immunosuppressive agent originally used in heart, liver and kidney transplant patients. The effects of oral cyclosporin in psoriasis were initially discovered in 1979[22] and subsequently confirmed in several clinical trials. These effects identified the immune system as a key player in the pathogenesis of psoriasis. Cyclosporin acts by inhibiting both the activation of T cells and the subsequent activation of keratinocytes by cytokines. Because of the potential side effects associated with long-term systemic cyclosporin use, treatment is usually reserved for severe, widespread or erythrodermic psoriasis, or patients who did not respond to other conventional therapies. Unfortunately, patients tend to relapse very quickly after cessation of treatment.[4] For almost 10 years patients with psoriasis and psoriatic arthritis of the countries of Western Europe such as Germany, Switzerland and France have been successfully treated with modern molecular-based, anti-cytokine therapeutic agents such as anti-TNF-α monoclonal antibody Adalimumab human, anti-IL-23, anti-IL-12 human monoclonal antibody Ustekinomab and others. These are agents, which are used with success in modern treatment in a number of severe debilitating autoimmune diseases such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis and juvenile idiopathic arthritis. The next generation of anti-cytokine therapies such as anti-IL-17 antibody and others in the treatment of psoriasis and psoriatic arthritis are in the process of clinical trials.

In Bulgaria there have been registered 4 such preparation, three of which are antagonists of tumor necrosis factor alpha (TNFα) (Infliximab, Adalimumab, Etanercept) and one is an antagonist of interleukin-12 (IL-12) and interleukin 23 (IL-23) (Ustekinumab).

Adalimumab is applied subcutaneously. The effect of treatment is reported in the 16th week and if there is no response the treatment is terminated. Upon discontinuation of treatment and subsequent resumption, the preparation can be expected to have less effect. The composition may be combined with Mtk to improve the therapeutic effect.

Etanercept is applied subcutaneously. The effect of treatment is reported in the third month and if one is missed, it must be terminated. Upon discontinuation of treatment and subsequent resumption, the preparation can be expected to have less effect. The composition may be combined with Mtk to improve the effect, especially in the presence of atrophic psoriasis.

Infliximab is the only formulation which is administered intravenously in a hospital setting due to the risk of reactions related to the infusion. Every three months the effect of treatment
is taken into account and if there is none, the treatment is discontinued. The composition may be combined with Mtk in case of a joint disease, for enhancing the effect or reducing the risk of formation of antibodies against Infliximab.

**Ustekinumab** is applied subcutaneously. The effect of treatment is taken into account by the 28th week and if one is missed, it must be terminated.\[^3\]

**CONCLUSIONS**

Treating of psoriasis is critical to good disease management and overall health. Team working to find a treatment—or treatments—that reduce or eliminate the symptoms are of great importance. It is very important to be taken in mind the fact that what works for one person with psoriasis might not work for another. So it's important to know the different treatment options and keep trying until finding the right treatment regimen for every single patients.

**Literature**


