MODERN UNDERSTANDING OF PSORIASIS*

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Abstract

Psoriasis is a chronic immune-associated disease of a multifactorial nature with a dominant role in the development of genetic factors. In 30% of patients, psoriasis is accompanied by the development of psoriatic arthritis (PsA), which can cause disability in patients and loss of function in the structures of the musculoskeletal system. Psoriasis affects 2-3% of the population. In most cases, the manifestation of psoriasis occurs at a young, socially active age, which adversely affects the patient's quality of life. Currently, the structure of conditions comorbid with psoriasis includes cardiovascular diseases, inflammatory diseases of the gastrointestinal tract, kidney diseases, cancer, metabolic syndrome, insulin resistance and diabetes mellitus, dyslipidemia, psychiatric comorbidity, neuroendocrine disorders, diseases of the hepatobiliary system. Given the variety of forms of psoriasis, treatment, the choice of treatment method depends on the severity of the psoriatic process, comorbidity, psychosocial burden associated with the disease, safety and patient preferences. A variety of methods are used to treat psoriasis, including topical medications, phototherapy, treatment with systemic and genetically engineered biological drugs.

Keywords: psoriasis, arthritis, multifactority, immune-associated, immunity, interleukin, tumor necrosis factor - alpha (TNF-α), keratinocytes, genes, heredity, comorbid, physiotherapy, phototherapy, genetically engineered biological drugs.

Psoriasis is a chronic immune-associated disease of a multifactorial nature with a dominant role in the development of genetic factors, characterized by accelerated proliferation of keratinocytes and impaired differentiation, an imbalance between pro-inflammatory and anti-inflammatory cytokines, with frequent pathological changes in the musculoskeletal system (Psoriasis. Clinical guidelines, 2020).

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Epidemiology

Psoriasis affects 2-3% of the population. The prevalence of psoriasis in the world varies depending on regions. Residents of the Caucasus and Scandinavia are most susceptible to the disease. In most cases, the manifestation of psoriasis occurs at a young, socially active age, which adversely affects the patient's quality of life. Among children, dermatosis is more common in girls than in boys. Psoriasis can occur in newborns and infants. Men and women get sick equally often. The onset of the disease in most cases occurs: before 10 years – in 11,6%, before 20 years – in 46%, before 30 years – in 61,6%. There are two peaks of incidence: in men – 27,5 and 54,5 years; for women – 15,5 and 54,5 years. According to several studies, 35-50% of patients have moderate to severe dermatosis. In 30% of patients, psoriasis is accompanied by the development of psoriatic arthritis (PsA), which can cause disability in patients and loss of function in the structures of the musculoskeletal system (Man, Man, Elias, 2015; Gladman et al. 2005; Menter, Gottlieb, Feldman et al., 2008).

Segregation analysis of the distribution of patients in families indicates multifactorial inheritance of psoriasis, with genetic and environmental components accounting for 60–70% and 30–40%, respectively. Possible forms of inheritance of psoriasis are of an autosomal dominant type with high gene penetrance (Parisi et al., 2013).

Etiology and pathogenesis

The etiology of psoriasis is unknown. The genetic factor plays a significant role in the pathogenesis of the disease. This is supported by the higher incidence of the disease among relatives of patients, which exceeds the average in the population, as well as the higher concordance of monozygotic twins (35–72%) compared to dizygotic twins (12–30%). The heritability of psoriasis is estimated at 60–90%, being one of the highest rates among multifactorial diseases of a genetic nature. The main marker of hyperproliferation keratinocytes in psoriatic lesions is an increased expression of the Ki67 protein and keratins 6, 16 and 17 types, providing hyperplasia of the epidermis with impaired differentiation of epithelial cells and the development of an inflammatory reaction in the dermis. The subpopulation of T lymphocytes – Th17 plays a major role in the development of the inflammatory process in psoriasis.

In psoriasis lesions, basal layer keratinocytes reach the skin surface within 6–8 days, whereas in healthy skin the maturation process takes about 40 days. Some genes normally expressed only in the basal layer (genes encoding integrins) of psoriatic skin are expressed in the thickened stratum spinosum. The following are expressed in the granular layer: psoriasis-associated fatty acid binding protein (FABP 5), filaggrin (FLG), corneodesmosin (CDSN), proteins involved in the formation of the stratum corneum (CE), etc., which can also be overexpressed in stratum corneum. Keratinocytes in patients with psoriasis produce many proteins – S-100 proteins (A7–A9, A12), encoded by EDC genes, as well as beta-defensins (CAM-1, CD40, IL-8, IP-10 and HLA-DR. Endothelial cell mitogens (VEGF, PDGF) are also synthesized, leading to the induction of angiogenesis. Consequently, inflammation in the skin is induced by products synthesized by keratinocytes. (Askhakov, Voronkova, 2014).

Data on the association and linkage of 20 genomic loci with various forms of psoriasis have been published, and within these loci a number of genes and chromosomes have been identified that are related to predisposition to psoriasis and encode participants in signaling pathways that play a role in the reactions of adaptive and innate immunity, and skin barrier function. The very first genetic locus associated with psoriasis was the HLAC gene, called PSORS1. Recent evidence suggests that the HLA-CW6 allele of the PSOR1 and HLADR7 locus is the basis of the genetic determinant of susceptibility to psoriasis.

The association of psoriasis with mutations in adaptive immunity genes involved in the implementation of signaling pathways involving Th lymphocytes: interleukin (IL)-12B, -13, -23A, IL-23R, IL-28RA receptor genes is also being studied. An association of IL-13 gene polymorphism with the risk of developing psoriasis and psoriatic arthritis was found. Insufficient expression of the product leads to increased activity of macrophages and the production of pro-inflammatory cytokines. Evidence has been obtained of the influence of the genetic component on the barrier function of the skin: 45 genes of the chromosomal region 1q21, located in the region of the PSORS4 locus, encode the epidermal differentiation complex (EDC), which plays a leading role in the functioning of epidermal cells. Many EDC genes are involved in the formation of psoriatic rashes. The cytokines IL-17, IL-20 and IL-22, produced by Th17 cells, were also detected in samples of affected skin. It has been established that mutations in the IFIH1 gene are key in the development of immune-mediated diseases. The known biological functions of IFIH1 support its role in psoriasis. IFIH1 is an interferon-induced RNA helicase that influences cell growth, differentiation and apoptosis, and is involved in the recognition of RNA viruses. It was found that the expression of IFIH1 is significantly increased in the epidermal cells of psoriatic plaques compared to healthy skin. The detected dermal gamma delta T cells are also involved in the immune process and play a more important role than Th1 and Th17 cells. These studies revealed the main links in the pathogenesis of psoriasis and made it possible to develop biological drugs (Bataille, Lens, Spector, 2012).

Oxidized low-density lipoproteins were found in large quantities in psoriatic plaques, metabolic disorders of essential fatty acids, lipoproteins, hyperproduction of free radicals and nitric oxide involved in the process of keratinization. Patients with severe psoriasis have a 1.9-fold increased risk of developing chronic kidney disease compared to the general population.

In the pathogenesis of psoriasis, genetic determination of disorders of lipid and carbohydrate metabolism has also been established. It has been shown that metabolic syndrome and hyperlipidemia in patients with psoriasis are detected much more often than in the average population. A high incidence of atherosclerosis and, as a consequence, cardiovascular complications was noted. Chronic inflammation and genetic determinants may be potential biological links underlying this association. It is assumed that pro-inflammatory cytokines contribute to both the formation of psoriasis and atherogenesis, peripheral insulin resistance, the development of arterial hypertension and type II diabetes mellitus.

Henseler T. and Christophers E., analyzing comorbidity data from more than 40,000 patients with psoriasis, report that some systemic disorders, such as diabetes, heart failure and obesity, are significantly more common in patients with psoriasis than in control subjects. Another global study assessing the prevalence of cardiovascular risk factors in 127,706 patients with mild psoriasis and 3,854 patients with severe psoriasis found that multiple cardiovascular risk factors were associated with psoriasis: diabetes, hypertension, hyperlipidemia, obesity and smoking. However, key components of the metabolic syndrome were more strongly associated with severe psoriasis than with mild psoriasis. In patients with widespread psoriasis in combination with metabolic syndrome, abdominal obesity, hyperleptinemia, hyperinsulinemia, insulin resistance, high oxidative potential with increased lipid peroxidation and decreased activity of antioxidant blood systems, as well as increased activity of pro-inflammatory cytokines are noted.

Currently, the structure of conditions comorbid with psoriasis includes cardiovascular diseases, inflammatory diseases of the gastrointestinal tract, kidney diseases, cancer, metabolic syndrome, insulin resistance and diabetes mellitus, dyslipidemia, psychiatric comorbidity, neuroendocrine disorders, diseases of the hepatobiliary system.

Available evidence suggests that the risk of non-alcoholic fatty liver disease (NAFLD) in patients with psoriasis is approximately 2 times higher than in the general population (48–59%).

It is important to note that the development of NAFLD in patients with psoriasis appears to occur regardless of exposure to potentially hepatotoxic antipsoriatic drugs such as methotrexate and anti-TNF agents. The results of several studies show that the combination of psoriasis and NAFLD can aggravate the course of both pathologies and contribute to the development of liver fibrosis (Lindsay, Fraser, Layton et al., 2009).

Diagnostics

The diagnosis of psoriasis is made based on the clinical picture of the disease. Patients complain of rashes, a feeling of skin tightness, and may experience itching of varying degrees of intensity.

To make a diagnosis, the main thing is to conduct a visual examination of the patient's skin. The rashes are characterized by the presence of a psoriatic triad, which represents the phenomena that sequentially appear when scraping papular rashes: stearin stain (with slight scraping of the papule, an increase in peeling is observed, giving the surface of the papules a resemblance to a crushed drop of stearin); terminal film (the appearance after complete removal of the scales of a wet, thin, shiny, translucent surface of the elements); pinpoint bleeding (the appearance of pinpoint blood droplets that do not merge with each other after careful scraping of the terminal film).

Treatment

Taking into account the variety of forms of psoriasis, the choice of treatment method depends on the severity of the psoriatic process, comorbidity , psychosocial load associated with the disease, safety and patient preferences. A variety of methods are used to treat psoriasis, including topical medications, phototherapy, and systemic treatment. For the treatment of mild forms of psoriasis, limited rashes, patients are recommended external therapy.

External therapy

Topical glucocorticosteroids are used (in the form of ointments, creams, sprays or lotions) for any form of psoriasis as monotherapy or in combination with other external or systemic agents.

For the treatment of psoriasis, the synthetic analogue of 1.25-dihydroxycholicaliferol (vitamin D3) – calcipotriol is more widely used. The mechanism of action of calcipotriol is based on interaction with specific receptors in keratinocytes, which causes inhibition of proliferation, accelerates the morphological differentiation of psoriatic cells, inhibits the activity of interleukin-1, reduces the production of interleukin-2, that is, it affects the pathogenetic mechanisms of psoriasis.

Preparations containing activated zinc pyrithione (aerosol, cream, ointment, shampoo) are used. In the stationary stage, patients with dense infiltrated plaques are recommended ichthammol, naftalan oil, birch tar, and for psoriasis of the scalp - clobetasol shampoo. In foreign clinical recommendations, local therapy also includes the use of retinoids (tazarotene), dithranol and topical calcineurin inhibitors.

Phototherapy

Methods of medium-wave phototherapy (UVB/UVB-311) and PUVA therapy methods are recommended. UVB therapy methods do not require the use of photosensitizers and can be used in children. PUVA therapy methods are based on the combined use of photosensitizers of the psoralens group and long-wave UV radiation with a wavelength of 320-400 nm (Psoriasis. Clinical Guidelines, 2020).

Systemic therapy

It is performed for moderate and severe forms of psoriasis. Common means of systemic therapy – cytostatic drugs (methotrexate, acitretin, cyclosporine, etc.) are prescribed mainly during the progression of the disease. Subsequently, in severe cases, maintenance therapy is carried out.

In the absence of clinical effect from the use of other systemic therapies (including cyclosporine, acitretin, methotrexate and PUVA therapy) or in cases of intolerance or contraindications to their

use in patients with widespread rashes (moderate to severe psoriasis), selective immunosuppressants (phosphodiesterase inhibitor) are recommended-4 apremilast, Janus kinase blocker tofacitinib), as well as immunosuppressants, which are genetically engineered biological drugs according to the production method - tumor necrosis factor alpha (TNF-alpha) inhibitors, interleukin inhibitors.

Adalimumab is a recombinant monoclonal antibody whose peptide sequence is identical to human IgG1. Adalimumab blocks the activity of TNF-α, a pro- inflammatory cytokine that plays a key role in the pathogenesis of psoriasis.

Apremilast (selective immunosuppressant) is a phosphodiesterase 4 (PDE4) inhibitor that acts intracellularly to modulate pro-inflammatory and anti-inflammatory mediators that are involved in the pathogenesis of psoriasis and psoriatic arthritis (PsA). Recommended for the treatment of severe and moderate plaque psoriasis in patients who are candidates for systemic therapy. The combined use of apremilast and UVB 311 therapy can be used to increase the effectiveness of therapy.

Guselkumab is a human monoclonal antibody that selectively binds to the interleukin 23 (IL-23) protein with high specificity and affinity. The clinical effects of guselkumab in plaque psoriasis are associated with blockade of the IL-23 cytokine pathway. Guselkumab is recommended for the treatment of severe to moderate plaque psoriasis in patients eligible for systemic therapy.

Ixekizumab is a humanized monoclonal antibody to the cytokine interleukin 17A from the subclass of immunoglobulins G4 (IgG4). Increased concentrations of IL-17A are involved in the pathogenesis of psoriasis through stimulation of proliferation and stimulation of keratinocytes, as well as in the pathogenesis of psoriatic arthritis. Ixekizumab is indicated for adult patients with moderate to severe psoriasis.

Infliximab is a chimeric murine-human monoclonal antibody that binds with high affinity to the soluble and transmembrane forms of TNF-α. The drug is indicated for the treatment of adult patients with psoriasis in the absence of clinical effect from the use of other systemic methods of therapy or in cases of intolerance or contraindications to their use, as well as for the treatment of active progressive psoriatic arthritis.

Netakimab is a recombinant humanized a monoclonal antibody that specifically binds interleukin-17A in therapeutic concentrations. In patients with psoriasis, the use of netakimab is accompanied by the extinction of inflammation and hyperkeratosis in the skin, a significant decrease in the level of C-reactive protein and ESR.

Secukinumab is a fully human antibody (immunoglobulin G1) that selectively binds to and neutralizes the proinflammatory cytokine interleukin-17A. A consequence of treatment with secukinumab is a decrease in the severity of redness, thickening and peeling of the skin, which is observed in lesions of plaque psoriasis.

Tofacitinib is a potent, selective inhibitor of the Janus kinase family with high selectivity for other kinases in the human genome. Tofacitinib is indicated for the treatment of adults with moderate to severe chronic plaque psoriasis when systemic therapy or phototherapy is indicated.

Ustekinumab is a fully human class IgG1k monoclonal antibody that has high affinity and specificity for the p40 subunit of the human interleukins (ILs) IL-12 and IL-23. The drug is indicated for the treatment of adults with moderate to severe plaque psoriasis, as well as patients with active psoriatic arthritis, as monotherapy or in combination with methotrexate.

Certolizumab pegol is an inhibitor of tumor necrosis factor alpha (TNFα), the main cytokine that supports the inflammatory process in psoriatic arthritis and psoriasis. Indicated for adults with moderate to severe psoriasis vulgaris who are candidates for systemic therapy, including patients with psoriatic arthritis. Certolizumab pegol can be prescribed throughout pregnancy, as well as during breastfeeding.

Etanercept – a tumor necrosis factor-alpha (TNF-alpha) inhibitor is indicated for adults with moderate to severe psoriasis. The combined use of etanercept and UVB-311 therapy can be used when the therapeutic response to monotherapy is reduced etanercept.

The criteria for the effectiveness of psoriasis therapy are the timing of the onset of clinical effect, the duration of remission, and improvement in the patient's quality of life. And index of area and severity of psoriatic lesions (Psoriasis Area and Severity Index [PASI]) remains the basic standard in dermatovenerology and is used to assess the severity of psoriasis and the effectiveness of therapy.

Sanatorium-resort treatment

Sanatorium-resort treatment is recommended during the stationary and regressive stages of the disease, as well as during remission. Erina I.A. demontrated the effectiveness of silt medium-sulfide mud in patients with psoriasis in combination with sodium chloride baths with mineral water and climatic factors was shown. Ayush Tsogtsetseg determined the normalizing effect of chemical elements of mud on immunological and morphological parameters in patients with psoriasis. After annual treatment for 3 years, stable clinical remission was achieved in 85-96% of patients.

A good therapeutic effect is achieved when treating psoriasis at the Archman balneological resort. Archman water belongs to the class of hydrogen sulfide, weakly mineralized and subthermal . It contains 24 elements included in the periodic system of Mendeleev. Muravenko A.A. developed a technology for the step-by-step treatment of patients with psoriasis using physiotherapeutic procedures at the Archman resort (Muravenko, 2020).

CONCLUSION

According to the latest data on the study of pathogenesis, psoriasis often leads to disability. When treating mild psoriasis, local therapy is sufficient to relieve the main symptoms of the disease. Patients with moderate to severe psoriasis require screening for comorbidities and systemic therapy. Thanks to the emergence of innovative biological drugs, it has become possible to significantly lengthen the period of remission of psoriasis, which is a definite achievement in the treatment of this disease.

LITERATURE

1. Bataille V, Lens M, Spector TD. The use of the twin model to investigate the genetics and epigenetics of skin diseases with genomic, transcriptomic and methylation data. J Eur Acad Dermatol Venereol. 2012 Sep;26(9):1067-73.

2. Gladman D, et al. Psoriatic arthritis: epidemiology, clinical features, course, and outcome, Ann. Rheum. Dis. 2005; 64:ii14.d.

3. Lindsay K., Fraser A., Layton A. et al. Liver fibrosis in patients with psoriasis and psoriatic arthritis on long-term, high cumulative dose methotrexate therapy. Rheumatology (Oxford). 2009;48 (5): 569–72.

4. Man MQ, Man G, Elias PM. Could psoriasis be preventable? Dermatologica Sinica. 2015;33(4):243–244.

5. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. J. Am. Acad. Dermatol. 2008; 58:826-850.

6. Parisi R, et al. Global Epidemiology of Psoriasis: A Systematic Review of Incidence and Prevalence. J. Invest. Dermatol. 2013;133:377-385.

7. Асхаков М.С., Воронкова Е.Б. Особенности генетического фактора в наследовании полигенных заболеваний кожи. Актуал. вопр. дерматовенерол., косметол. и курортол.: сб. матер. Ставрополь, 2014. С. 40–43.

8. Муравенко, А.А. Природные факторы курорта Арчман в лечении и реабилитации больных псориазом. Актуальные проблемы санаторно-курортного лечения: сб. науч-практич. работ, посвящённых 40-летию ОАО «Белагроздравница» и 25-летию филиала Санаторий «Радон» ОАО «Белагроздравница». УО «Гродненский гос. Мед. университет». Гродно, 2020. С. 252-256.

9. Псориаз. Клинические рекомендации. Общероссийская общественная организация «Российское общество дерматовенерологов и косметологов». Год утверждения:2020.