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Targeted therapy of psoriatic disease

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Psoriasis is one of the most common dermatological diseases that affects about 5% of the world's population. The disease occurs in all age groups, it is often characterized by continuously-recurrent course and significantly worsens patient's quality of life. Despite the numerous studies conducted in different countries around the world, the pathogenesis of the disease has been studied insufficiently. Currently, immune system regulation disorders through complex mechanisms of keratinocyte interaction with the cells of the congenital and adaptive immunity system are believed to play the main role. Further, the severity and outcome of the disease depend on the severity of immunological disorders and imbalance of cytokine regulation of intercellular interactions. Immunologic preparations are the main therapy for psoriasis and its most severe form, psoriatic arthritis. Genetically engineered biological preparations, monoclonal antibodies, specifically those blocking certain pro-inflammatory cytokines or immunocompetent cells, are the most modern of them. This group of drugs is used to treat severe psoriasis, especially in combination with joint diseases, and in the case of ineffective conventional therapy. Implementation of innovative biological preparations in the treatment of patients with psoriasis enabled significant prolongation of disease remission and made a breakthrough in dermatology.

Keywords: *psoriasis, psoriatic arthritis, pathogenesis, cytokines, genetically engineered biological preparations.*

Psoriasis is the most common chronic skin disease. It is a topical problem of modern medicine. Psoriasis affects up to 5% of the world's population [1, 2]. The highest incidence is observed in Western Europe and Scandinavia; the disease is less common in Negroid and Mongoloid races. Psoriasis can occur at any age, from the neonatal period to advanced years [3, 4]. Childhood dermatosis is more common in girls. In most cases, the disease manifests in children and young population: 11.6% — below 10 years, 46% — below 20%, 61.6% — below 30 years [5].

Psoriasis is a multifactorial disease with high proportion of genetic component and various homeostatic disorders (Fig. 1).

It is currently known that the genetic component accounts for 60—70% in the development of psoriasis, while environmental factors account for about 40%. Psoriasis belongs to polygenic disease, where the same phenotype can be determined by different genes. To date, more than 100 genes located on eight different chromosomes associated with the development of psoriasis have been identified. These gene loci are known as Psoriasis Susceptibility Genes (PSORS) [6].

Currently, psoriasis is considered as a systemic disease with variable symptoms. Clinical manifestations of psoriasis are extremely diverse and can vary in wide range: from isolated skin lesions to severe systemic forms that are fatal. It has been found that psoriasis is accompanied by progressive disorganization of the connective tissue in combination with systemic proliferative-destructive vasculitis, leading to the development of visceral disorders [7]. Pathological process may involve the digestive tract, hepatobiliary, cardiovascular, urinary, nervous, and musculoskeletal systems.

Psoriatic arthritis (PsA) is one of the most severe clinical manifestations. According to different authors, the incidence of arthritis in patients with psoriasis ranges from 13.5 to 47% [8]. PsA is a chronic progressive systemic inflammatory process associated with psoriasis, which is mostly localized in the tissues of the musculoskeletal system and leads to the development of erosive arthritis, intra-articular osteolysis, and spondylarthritis [9].

Five clinical subtypes of PsA are distinguished [10]:

1. Asymmetric oligoarthritis (70%);
2. Mutilating arthritis (5%);
3. Arthritis of the distal interphalangeal joints of the hands and feet (5%);
4. Rheumatoid polyarthritis (15%);
5. Psoriatic spondylitis (5%).

In most cases, PsA develops gradually, acute form is much less common. In most patients, skin rash occurs before involvement of the joints, spine, or entheses. Characteristic features of the disease include arthritis of the distal interphalangeal joints of the hands and feet, axial arthritis (simultaneous involvement of three joints of one finger), dactylitis (inflammation of the finger with concomitant involvement of tendons and joints), "sausage" and "radish" finger deformities. Acute dactylitis is considered to be an unfavorable prognostic factor in terms of the development of erosions and osteolysis. Enthesites, sacroiliitis, and spondylitis are often detected.

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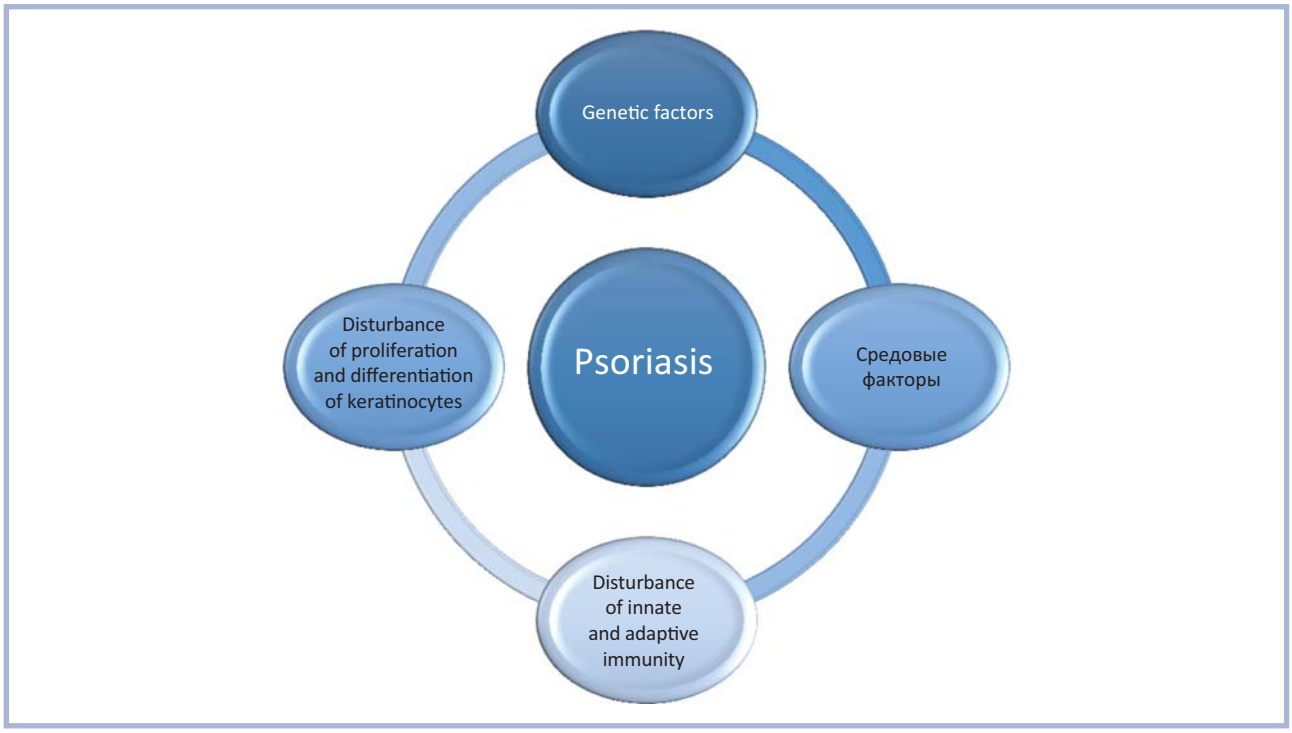

Fig.1. **Etiology of psoriasis.**

PsA is often comparable to rheumatoid arthritis and Bechterew's disease in terms of its clinical presentation and prognosis, which necessitates active and expensive therapy aimed at achieving remission or reducing the rate of disease progression. The diagnosis of PsA is based on the presence of a number of symptoms, such as psoriatic lesions of the skin or nails in a patient or his/her blood relatives. The absence of skin process poses certain difficulties: in these cases, the patient should be carefully examined in order to find even minimal signs of psoriasis [11, 12].

Psoriasis significantly worsens patient' quality of life. Physical and moral suffering of patients with psoriasis are comparable to those with cancer, cardiovascular, endocrine, rheumatic, and mental diseases [13].

The pathogenesis of psoriasis is extremely complex and not fully understood. Several theories of pathogenesis were changed during the study of the disease (Table 1).

The leading role of immune-mediated inflammation implemented through complex mechanisms of interaction between keratinocytes and the cells of congenital (myeloid and plasmacytic cells, dendritic cells, macrophages, NK and NK T cells) and adaptive (T lymphocytes) immunity have been established. The severity and outcome of the disease depend on the severity of immunological disorders and imbalance of cytokine regulation of intercellular interactions [14, 15].

Immunological disorders associated with psoriasis are based on activation of cellular immune response with leading role of T lymphocytes. Depending on the secreted factors, T lymphocytes are classified into Th_1 cells that produce cytokines IL-2, IFNγ, and TNFα, inducing cell-mediated immune response; Th_2 cells that produce IL-4, IL-5, IL-6, IL-10, IL-13, leading to the development of humoral immune response; Th_{17}, the pathogenetic CD4+ T cell line described in 2005. Th_{17} lymphocytes synthesize a wide range of cytokines, primarily IL-17A, IL-17F, IL-6, IL-21, IL-22, and TNFα. These cells play a key role in anti-infective protection, primarily against extracellular pathogens that cannot be effectively eliminated by type 1 and 2 T-helpers, as well as in the development of autoimmune diseases and in regulation of antitumor immune response [16—20].

In recent years, T-regulatory cells are believed to be of great importance in the development of psoriasis; the main function of these cells is to provide immunological tolerance and limit the immune response. Psoriasis is associated with deficiency or dysfunction of regulatory T cells, which ultimately leads to formation of inadequate immune response and is accompanied by activation of the Th_1- and Th_{17}-mediated immune response [21].

Currently, psoriasis is considered as an autoimmune disease, which is based on activation of Th_1 lymphocytes with hyperproduction of pro-inflammatory cytokines TNF-α, IFN-γ, IL-17, and IL-22 and relative decrease in expression of cytokines produced by Th_2 lymphocytes [22]. Th_{17} lymphocytes, whose number increases dramatically inside the lesion, which is accompanied by formation of characteristic morphological changes in the epidermis and dermis, are also believed to play a significant role in psoriasis. Th_{17} lymphocytes secrete proinflammatory cytokines in the skin, including TNFα, IL-17, IL-22,

Table 1. **Evolution of immunopathogenesis of psoriasis.**

Theory	Years	Basic therapy
Keratinocyte dysfunction	Until the 1980s	Methotrexate PUVA-therapy Retinoids
Immunological	1980s	Cyclosporin
Th_1-mediated disease	1990–2008	Alefacept Efalizumab TNF-α blockers,
IL-23/Th_{17} mediated disease	From 2009 to the present	Ustekinumab Secukinumab Brodalumab Guselkumab Tildrakizumab Risankizumab

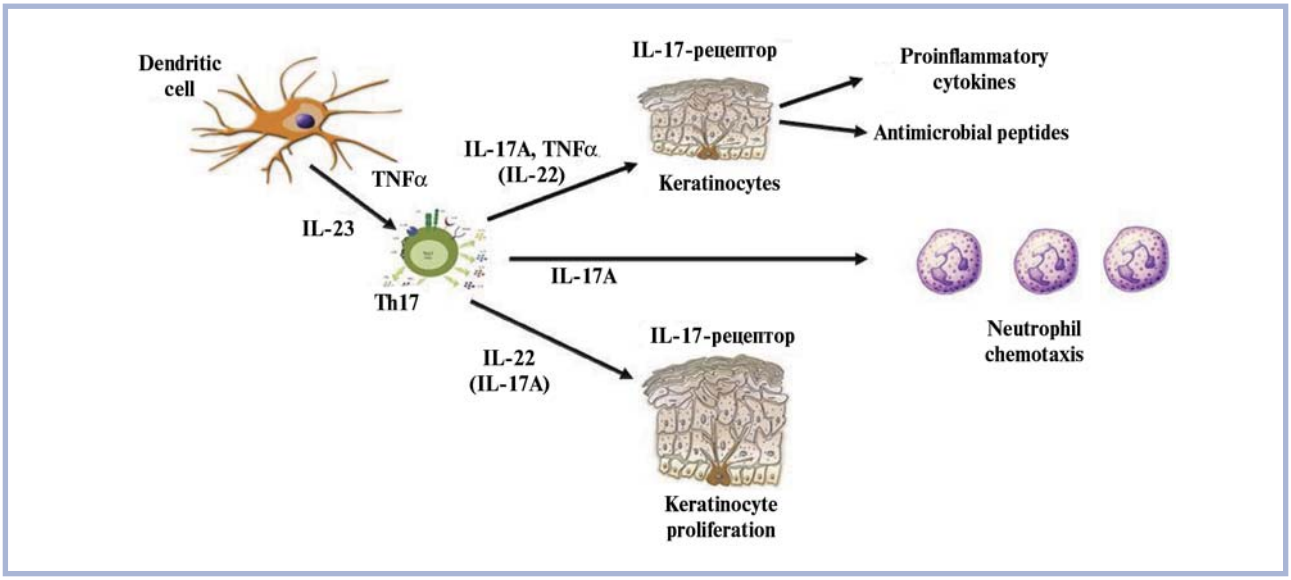

Fig. 2. **IL-23 production.**

IL-23, and others, which play a key role in pathogenesis of psoriasis, and also stimulate angiogenesis and migration of neutrophils [23, 24].

Along with Th cells, significant role in the pathogenesis of PS and PsA is played by myeloid dendritic cells producing increased amount of IL-12 and IL-23 in psoriatic dermis, which in turn lead to activation of T lymphocytes followed by their differentiation into subpopulations 1 and 17 of T-helper cells (Th_1 and Th_{17}) with characteristic set of cytokines, including IL-17, inducing IL-6, IL-8, and other inflammatory proteins in keratinocytes (Fig. 2) [22].

Additionally, IL-23 has been shown to increase proliferation and disturb differentiation of keratinocytes, which leads to formation of acanthosis in the epidermis and characteristic psoriatic skin lesions and plays an important role in the development of psoriatic arthritis [25].

Imbalance of pro- inflammatory and anti-inflammatory cytokines is the key element in the immunopathogenesis of psoriasis. This disease is associated with increased expression of IL-1β, IL-6, IL-10, IL-2, IL-8, IL-12, IL-15, IL-17, IL-22, IL-23, TNFα, IFNγ, and IFNα. TNFα is one of the key cytokines triggering immunopathological reactions in psoriasis. It is characterized by extremely wide range of biological effects [26, 27]:

— increases expression of cellular and vascular adhesion molecules-1, which are involved in migration of lymphocytes to the inflammation site;

— activates lymphocytes and fibroblast proliferation;

— stimulates synthesis of leukotrienes, prostaglandins, nitric oxide, and matrix metalloproteinases, in particular collagenase, stromelysin, and gelatinase, inducing cartilage and bone destruction

TNFα regulates activity of genes encoding the synthesis of cytokines, such as IL-1, IFNγ, GM-CSF, IL-6, pro-inflammatory chemokine IL-8, as well as other inflammatory mediators, by activating transcription factors. During development of inflammation, TNFα acts on hepatocytes and thereby regulates the acute phase response, increasing the content of C-reactive and other acute phase proteins. TNFα induces the synthesis of free

oxygen radicals and inhibits apoptosis of inflammatory cells. Additionally, TNFα is actively involved in bone remodeling, enhancing osteoclastogenesis, and may be responsible for the development of intra-articular osteolysis, a characteristic symptom of PsA [28, 29].

IL-17 also plays an important role in the development of immunological inflammation in patients with psoriasis. The IL-17 family includes IL-17A, B, C, D, E, F, whose main function is to activate the synthesis of pro-inflammatory cytokines. The physiological role of IL-17 is to protect the body against bacterial and fungal infections. In the case of psoriasis, interaction between IL-17 and its receptors leads to induction of expression of pro-inflammatory cytokines, chemokines, adhesion molecules, and growth factors, which results in progression of the immune inflammatory process [30]. The role of IL-21 is to maintain the Th_{17}-cell balance. This cytokine increases expression of the receptors for IL-23 (IL-23R) on T lymphocytes arriving to the inflammation site, thereby facilitating involvement of new Th_{17} cells into the pathological process [31].

In patients with psoriasis, IL-22, which is produced by Th_{17} and Th_{22} lymphocytes, disturbs terminal differentiation of keratinocytes, causing characteristic abnormalities in the epidermis. Moreover, the level of IL-22 correlates with the severity of the process in patients with psoriasis [32]. IL-6, a pleiotropic proinflammatory cytokine, which synergistically interacts with IL-1 and TNFα and thereby causes hyperproliferation of the epidermal growth factor and promotes hyperproliferation of epidermal cells [33], plays a certain role in the immunogenesis of psoriasis. Chemokine IL-8 contributes to chemotaxis and infiltration of the dermis with neutrophils. Neutrophils synthesize IL-1β, IL-6, IL-8, IL-17, and TNF-α. In turn, IL-17A, IL-17F, and TNF-α synthesized by neutrophils and other immune cells induce IL-8 synthesis in keratinocytes, causing neutrophil influx into the epidermis. In the epidermis, neutrophils stay in close contact with keratinocytes, myeloid dendritic cells, and NK cells. These contacts significantly increase resistance of neutrophils to apoptosis. An important role in the development of inflammation in psoriasis is attributed to IFNγ, resulting in lymphocyte infiltration of psoriatic plaques [34].

Thus, literature data show the important role of the immune system in the development of psoriasis. In connection with the immuno-mediated nature of psoriasis, administration of drugs affecting the immune system is pathogenetically justified. Administration of methotrexate, cyclosporine A, thymodepressin, cycloferon was found to be effective, but serious adverse reactions could not be avoided in all cases. Along with changes in the liver, myelosuppression, pulmonary fibrosis, involvement of kidneys and nervous system are the most serious complications of immunosuppressive therapy [35].

The thesis of the autoimmune nature of psoriasis gave a rise to rapid development of genetically engineered biotechnologies, which enabled radical reconsideration of approaches to the treatment of this disease. The "biological" strategy based on the principle of targeted blockage of pro-inflammatory cytokines or immunocompetent cells with their specific inhibitors was a breakthrough in the treatment of psoriasis [2]. Anti-cytokine therapy for psoriasis involves the following areas:

— elimination of abnormal T cells;

— blockage of T cell activation or their migration into the tissue;

— immune correction to alter the effects of cytokines (increasing the level of Th_2 cytokines to normalize the Th_1/Th_2 imbalance);

— inflammatory cytokine binding.

Biological preparations are monoclonal antibodies (MABs) developed using genetic engineering methods and used for therapeutic purposes. There are several types of MABs. Their names end in "-mab" (monoclonal antibodies): infliximab, adalimumab, etc. Additional letters in the endings of drug names are used to distinguishing the source of these antibodies:

— MABs from rodents end in -omab;

— chimeric — -ximab;

— humanized — -zumab;

— recombinant human — -umab.

It is believed that therapy with genetically engineered biological products (GEBPs) should be considered in those cases where the preliminary basic treatment was ineffective during the planned period of administration (usually 3—6 months) and the estimated minimum activity of the disease was not achieved [36]. This group includes a large number of drugs (Table 2).

Currently, four GEBPs are used in the Russian Federation to treat psoriasis: infliximab, adalimumab, etanercept, and ustekinumab (Fig. 3) [37].

Infliximab was the first anti-cytokine drug used to treat psoriasis. In the Russian Federation, it has been officially approved in PsA patients since 2005 and used to treat moderate to severe plaque psoriasis since 2006. It is a selective TNFα antagonist represented by chimeric *IgG* MABs, consisting of 75% human and 25% murine protein. The drug causes apoptosis of activated T lymphocytes and keratinocytes of the skin, reduces inflammation and angiogenesis in psoriatic plaques. Infliximab forms stable compounds with TNFα, significantly reducing its functional activity. The drug is indicated for treatment of adult patients with psoriasis in the cases when the use of other systemic therapies is ineffective or there is intolerance or contraindications to their use, as well as for the treatment of active progressive PsA. When treating PsA, the drug can be used in combination with methotrexate. The initial dose of infliximab for treatment of psoriasis and PsA is 5 mg per kg of the patient's body weight. Infliximab is administered in the form of intravenous infusion for 2 hours at a rate of no more than 2 ml/min. Blood pressure, heart rate, frequency of respiratory movements, and body temperature should be measured every 30 minutes during intravenous infusion of the drug.

Table 2. **Genetically engineered biological preparations**

Drug product		Application	Manufacturer
INN	Trade name		
Adalimumab	Humira	Anti-TNFα MAT	Abbvie
Alefacept	Amevive	Antagonist of CD2-binding fragment	BiogenIdec
Apremilast	Otezla	Inhibitor of PDE-4	Celgene
Briakinumab	Ozespa	Anti-IL-12 and IL-23 MAB	Abbott
Brodalumab	Siliq	Anti-IL-17 MAB	Valeant
Golimumab	Simponi	Anti-TNFα MAB	BaxterPharmaceuticalSolutions
Guselkumab	Tremfya	Anti-IL-23 MAB	Johnson & Johnson
Ixekizumab	Taltz	Anti-IL-17 MAB	Eli Lilly
Infliximab	Remicade	Anti-TNFα MAB	Johnson & Johnson
Risankizumab	-	Anti-IL-23 MAB	Abbvie
Secukinumab	Cosentyx	Anti-IL-17 MAB	Novartis
Tildrakizumab	-	Anti-IL-23 MAB	SunPharmaceuticalIndustries
Tocilizumab	Actemra	Anti-IL-6 MAB	ChugaiPharmaManufacturing
Ustekinumab	Stelara	Anti-IL-12 and IL-23 MAB	Johnson & Johnson
Certolizumab pegol	Simzia	Anti-TNFα MAB	UCB Pharma SA
Etanercept	Enbrel	TNFα inhibitor	Amgen
Efalizumab	Raptiva	MAB to CD11a antigen.	GenetechXomaSeronoGEBPs

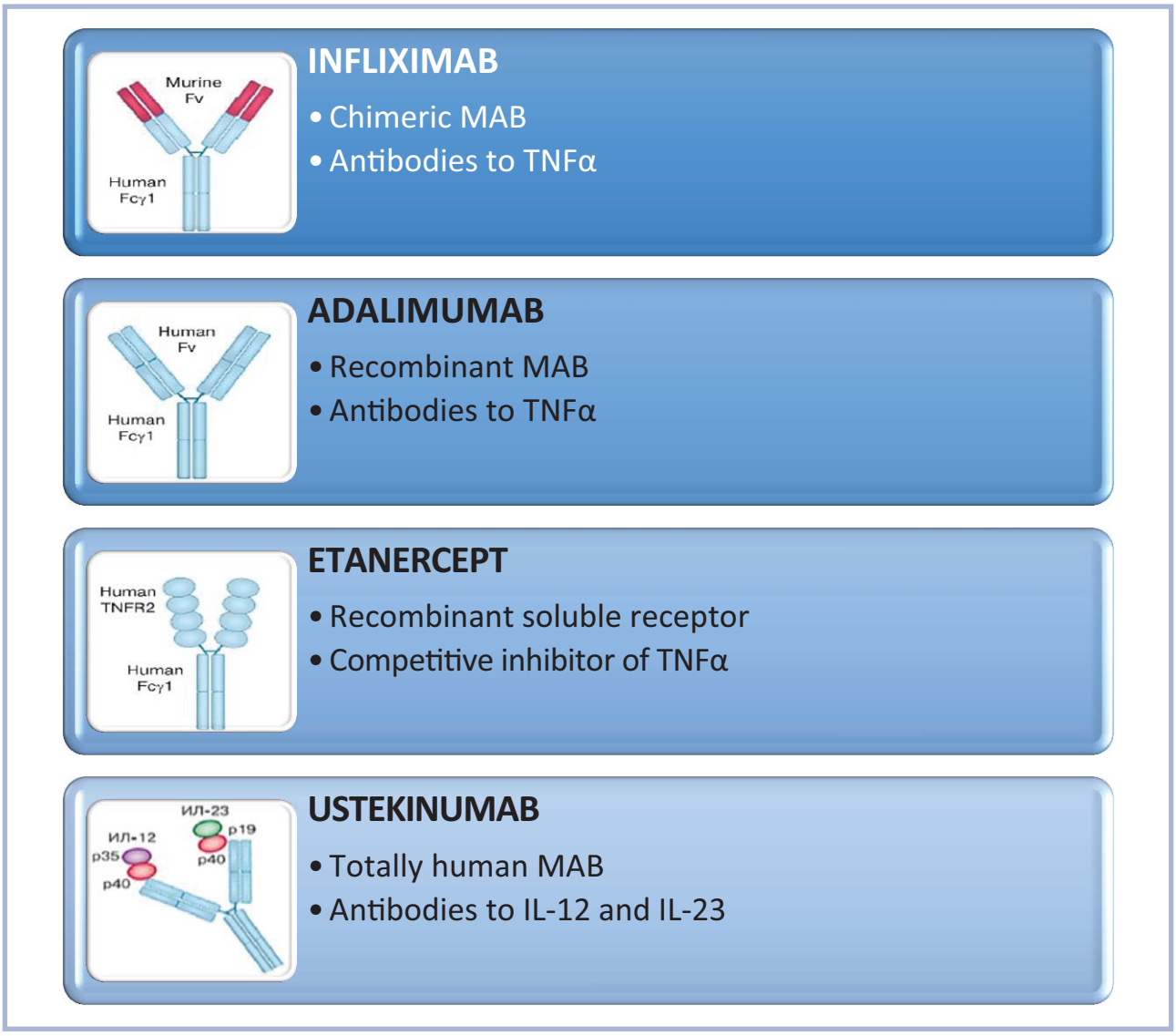

Fig. 3. **GEBP registered in the Russian Federation.**

The patient must be under medical supervision during intravenous infusion and for 1—2 hours after its termination. The first injection of the drug is followed by administration of the same dose in 2 and 6 weeks, and then every 8 weeks. Clinical experience of application of infliximab by Russian dermatologists shows high efficacy of the drug as evidenced by active regression of clinical manifestations of the disease and improvement of patient's quality of life [38].

Adalimumab is a selective immunosuppressive agent, which is completely identical to human MABs, blocking the activity of TNFα, a proinflammatory cytokine that plays a key role in the pathogenesis of psoriasis [39]. The drug demonstrates clinical and radiological efficacy, regardless of whether or not the patient has previously received methotrexate. Among the group of TNFα inhibitors, adalimumab is characterized by good tolerability and low incidence of adverse reactions. Adalimumab is administered by subcutaneous injections in the thigh or abdomen. The initial dose for adult patients with chronic plaque psoriasis is 80 mg; maintenance dose — 40 mg once per 2 weeks, starting a week after the initial dose.

Etanercept is the first TNFα inhibitor approved by the US Food and Drug Administration (FDA) in 2002 for the treatment of psoriasis and PsA. It binds to soluble and transmembrane TNFα molecules and neutralizes them. Additionally, the drug disturbs migration of neutrophils, dendritic cells, and T lymphocytes, thereby reducing systemic production of pro-inflammatory cytokines and their subsequent effects. Long-term treatment of PsA patients with etanercept led to decrease in radiological signs of joint disease progression. The drug is applied subcutaneously at a dose of 50 mg 2 times a week for 3 months followed by maintenance regimen, which includes injection of the same dose once per week. The drug is well tolerated by patients even during long-term treatment. Rare undesirable consequences include local reactions in the form of hyperemia and infiltration, infectious complications, myocardial infarction, depression, and basal cell carcinoma [8, 40].

Infliximab, adalimumab, and etanercept are TNFα inhibitors that are recommended for treatment of patients with moderate to severe psoriasis and active PsA [41]. Since TNFα is involved in early stages of the inflammatory process, being an active pro-inflammatory agent and a key one in the cytokine cascade, TNFα blocking drugs have a universal mechanism of action: they stimulate T cell activation and induce expression of IL-2, IFNγ, pro-inflammatory cytokines (IL-1 and IL-12), and proinflammatory chemokines (IL-8). However, it is the universal mechanism of action that determines the development of such complications as systemic immunosuppression, body's defenselessness against infections (tuberculosis, inflammatory lung diseases, reactivation of chronic viral hepatitis C and B, soft tissue infections, herpes infection, candidiasis and other mycoses), and neoplastic processes. Additionally, antibodies to these drugs can be eventually produced, which leads to decrease in their effectiveness.

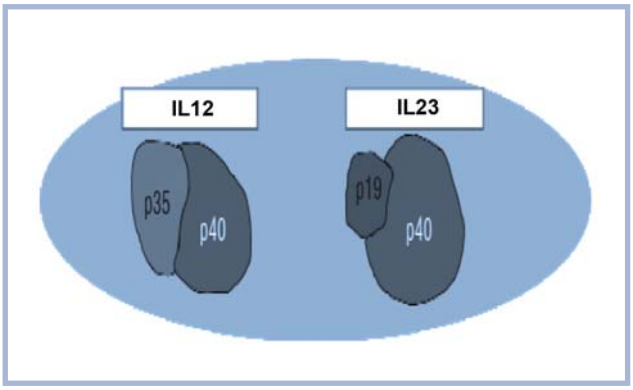

Fig. 4. **The structure of IL-12 and IL-23 (Korsakova Yu.L., Stanislav ML).**

The mechanism of action of **Ustekinumab,** which is an inhibitor of pro-inflammatory IL-12 and IL-23, differs from that of TNFα blockers. These are fully human *IgG1k* MABs, which have a high affinity and specificity to p40 subunit of IL-12 and IL-23 (Fig. 4).

This reduces production of pro-inflammatory cytokines by Th_1 and Th_{17} lymphocytes and, as a result, stops the cascade of inflammatory reactions at the earlier stage of the pathogenesis of psoriasis (Fig. 5) [42, 43]. The use of ustekinumab reduces hyperplasia of epidermal cell proliferation without significant effect on the ratio of immune cells circulating in the blood and the concentration of cytokines.

Ustekinumab is registered in the Russian Federation for treatment of moderate to severe plaque psoriasis, as well as patients with active PsA as monotherapy or in combination with methotrexate. Currently, the data on the efficacy and safety of continuous therapy with ustekinumab for 5 years in patients with medium to severe psoriasis are available. Ustekinumab is intended for subcutaneous injection in patients older than 18 years. The recommended dose is 45 mg. The second injection is given 4 weeks after the first one and then every 12 weeks. In patients with body weight of more than 100 kg, it is recommended to use the drug at a dose of 90 mg. Ustekinumab differs from other biological products in its high safety profile, rare severe side effects and complications. Thus, according to the large registry of biological drugs PSOLAR, patients with psoriasis demonstrated no increase in the risk of severe infections during monotherapy with ustekinumab compared to the use of TNFα inhibitors. Summarized data of five phase III clinical studies showed that there were no cases of activation of infectious process in 167 patients with psoriasis and latent tuberculosis, who received therapy with ustekinumab. The most frequent adverse effects include infections of the upper respiratory tract, nasopharyngitis, faryngolaryngeal pain, increase in creatine phosphokinase and lymphopenia, headache, and dizziness. Diarrhea, back pain,

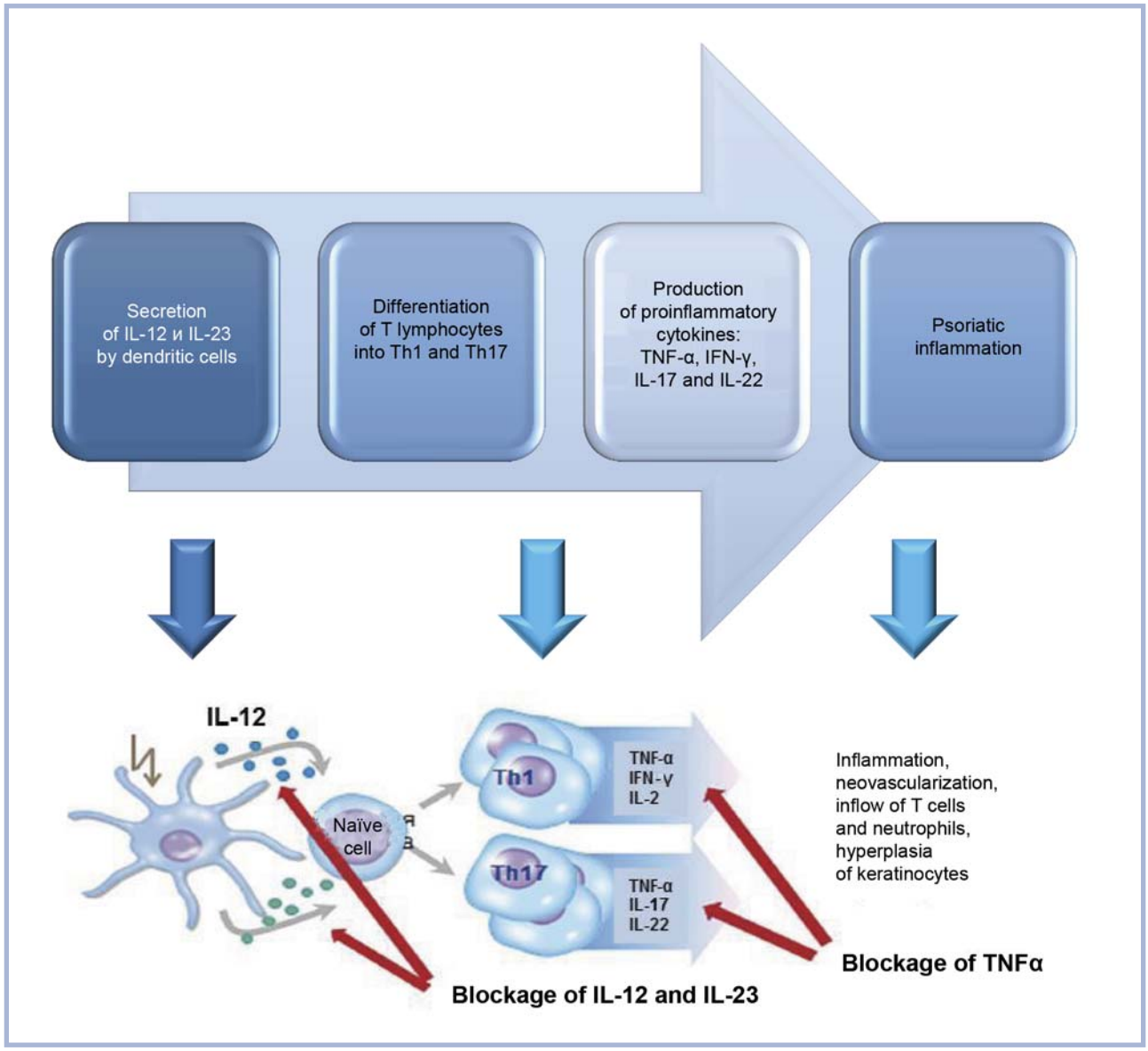

Fig. 5. **Points of application of GEBPs (Sokolovskiy EV, Kruglova LS).**

myalgia, and erythema at injection sites are quite rare complications.

Furthermore, ustekinumab was shown to be a low-immunogenic drug, since only 5% of patients formed specific antibodies in response to its administration. As a comparison, antibodies to infliximab were detected in almost 20% of patients in clinical studies of infliximab.

The new drug product **risankizumab**, selectively blocking IL-23 by binding to its p19 subunit, is currently undergoing stage III clinical trials. IL-23 is a proinflammatory cytokine, which plays an important role in the pathogenesis of psoriasis by inducing and supporting T helper 17 cells (Th_{17}), T helper 22 cells (Th_{22}), natural lymphocytes and effector cytokines IL-17, IL-22, and TNFα. The drug is administered subcutaneously at a dose of 90 or 180 mg (initial dose, weeks 4 and 16). In clinical trials, risankizumab demonstrated higher efficacy compared to ustekinumab and placebo. Additionally, the drug has higher safety profile compared to ustekinumab. According to preliminary findings, selective blockade of IL-23 by inhibition of the p19 rather than p40 subunit provides longer inhibition of IL-23 activity, which leads to more effective treatment of psoriasis.

There are two stages of GEBP application: induction and maintenance therapy (Table 3).

To date, quite extensive experience in using GEBPs has been accumulated in the Russian Federation, which revealed some limitations, such as primary ineffectiveness, "escape effect", and development of side effects of GEBPs. Safety of the use of GEBP in combination with systemic cytostatic agents enable developing the process of changing from one drug to another.

The development of primary ineffectiveness due to genetic characteristics of the recipient can be overcome

Table 3. **Stages of GEBP application**

Stage	Goal	Duration
Induction	Determine the efficacy and decide on the advisability of long-term administration	The first 12–28 weeks
Supportive therapy	Maintaining stable and prolonged remission	Several weeks to several years

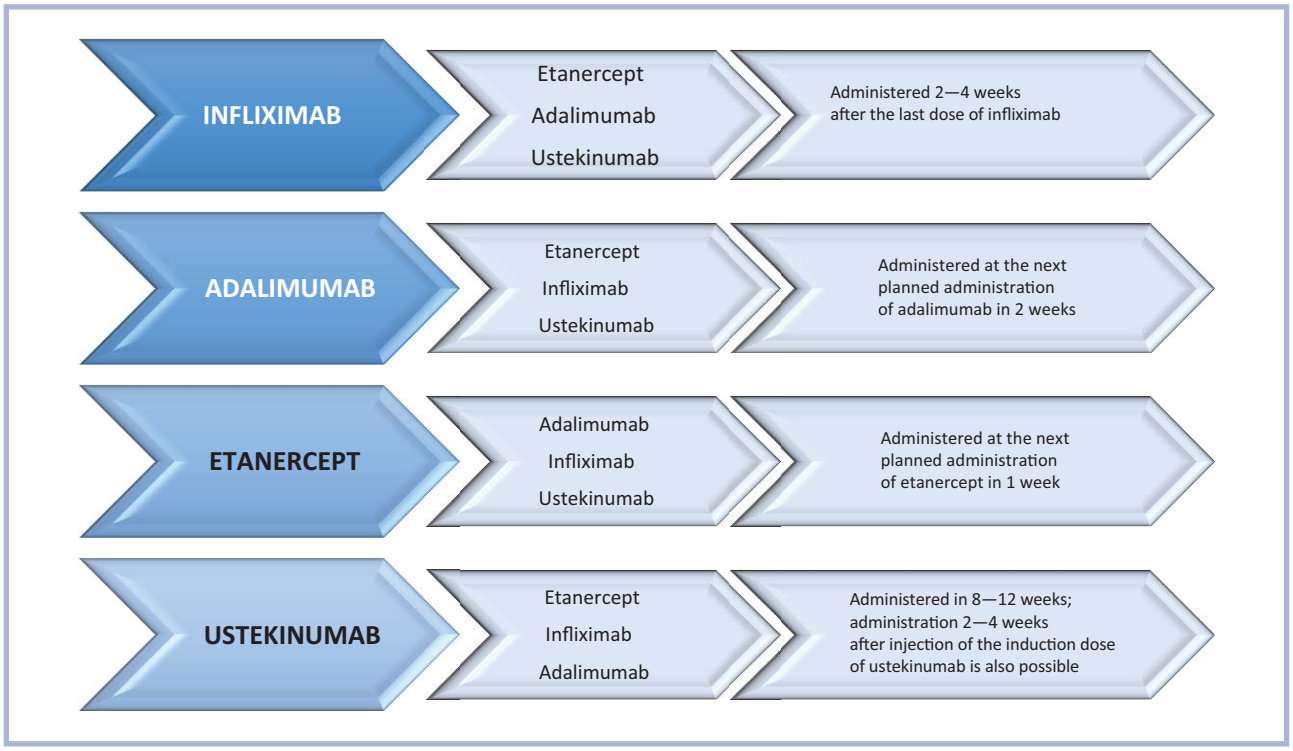

Fig.6. **Change from one GEBP preparation to another.**

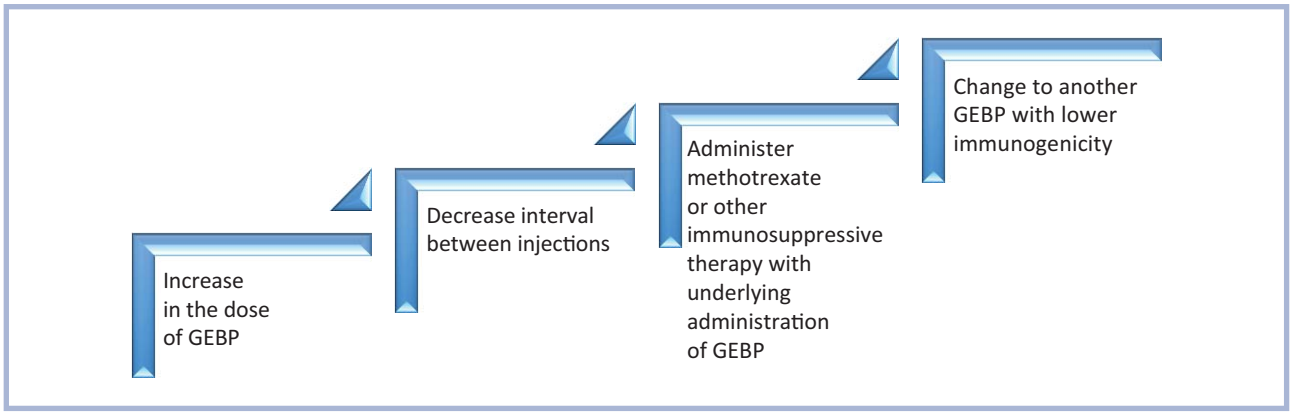

Fig. 7. Overcoming the "escape effect"

by changing the dose or dosage regimen of the GEBP, combination with low doses of methotrexate, or changing from one GEBP to another (Fig. 6).

The development of the "secondary ineffectiveness" or "escape effect" is also possible, which is mainly caused by production of neutralizing antibodies to the drug by the recipient's body. This mostly concerns TNFα inhibitors, especially in the case of long-term application [44, 45]. Thus, the results of numerous studies showed that almost a third of patients who received infliximab during a year demonstrated decrease in the effectiveness of therapy by 30%. A different picture is observed when using ustekinumab, which demonstrated stable effect for 5 years [46]. A series of step-by-step measures is recommended for correction of "escape effect" (Fig. 7).

In the case of concomitant administration of GEBP and methotrexate or cyclosporine, it is recommended to monitor all safety parameters as for each individual

Table 4. Different approaches to treatment of psoriasis

Effects on the immune system	Expected effect
Broad: methotrexate, cyclosporine A	Supposedly safe and/or less effective
Local: TNF-α	Less safe and more effective
Targeted: IL-23, IL-17A, IL-17RA	Probably highly safe and the most effective

monotherapy. More stringent intervals should be chosen for monitoring of safety parameters. When increase in toxicity is expected, monitoring intervals can be reduced and additional parameters can be added [47, 48].

Modern medicine has a large repertoire of drug products that differ in specificity and targeted action on the immune system (Table 4).

However, severe forms of psoriasis necessitate an integrated approach to therapy. The development of innovative biological products enabled significant increase in duration of remission of psoriasis. This fact gives hope that this incurable disease can be overcome. Novel more effective and safe drugs with more targeted mechanism of action will be discovered in the near future.

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