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Immunosuppressive drugs in dermatology – benefits and threats

Owing to the development of modern technique, scientists have proved that etiology of many diseases, also in dermatology, is connected with immunity disorders. Therefore, immunosuppression, used for thirty years in transplantology, has become very promising. It consists in breaking different immune reactions (for example, the inhibition of cell division or suppression of clonal cell expansion). According to the mechanism of activity, the immunosuppressive drugs reveal effects on each stage of the immunological process. Toxicity and side effects of these drugs also vary. The aim of our study is to show the connection between the immune mechanism of the disease and propriety of treatment and possible side effects.

Glycocorticosteroids are those immunosuppressive drugs that have been used for a long time. Due to their lipophilic nature, steroids diffuse freely through the cell membrane and bind to specific cytosolic receptors. Hormone-receptor complexes translocate to the nucleus and regulate, either positively or negatively, the expression of numerous genes. They may bind to transcriptive factors blocking their connection to DNA and, indirectly, the expression of genes. The synthesis of cytokines: IL-1, IL-3, IL-4, IL-6, IL-8, TNFα, GM-CSF and effects of IL-2, TNFα and IFNγ action are decreased by glucocorticosteroids, for example by checking IL-2 receptor expression) (11). T cell proliferation and differentiation is made impossible (7). Leucocyte redistribution into spleen and bone marrow is influenced by steroids. Hence, the number of lymphocytes, eosinophilic and basophilic granulocytes is decreased in blood circulation. The level of monocytes and their ability to synthesize IL-1 is lowered. Steroids inhibit the production of nitrogen oxide (NO) in macrophages and abate permeability of blood vessels by blocking mediators responsible for vessel dilatation (15). The synthesis of MHC I and II molecules, and the activity of directly antigen presenting cells, B and T cells is handicapped. The expression of adhesive molecules on the surface of various cells is also decreased. The level of IgA, IgG and IgM antibodies is lowered because of their decreasing synthesis or excessive catabolism. Anti-inflammatory effect is caused by breaking of inflammatory mediator production or synthesis of enzymes that inactivate these mediators. The synthesis of specific proteins (lipocortines) is increased by glycosteroids. These proteins bind to cell membrane phospholipides, and thus inhibit phospholipase A and, indirectly, PG, TX and LT activity (11). A wide variety of side effects related to steroids is the consequence of the lack of immunosuppressive, anti-inflammatory and metabolic activity. Increased natrium and water retention leads to high blood pressure and oedemas (11). Heart failures are the consequence of potassium loss. Owing to connective tissue protein catabolism the risk of osteoporosis and muscular atrophy is increased (12). Diabetogenic activity (the result of excessively activated gluconeogenesis) leads to diabetes melitus and decreases glucose tolerance. Obesity, striae of the skin and growth retardation in children are the result of metabolic disorders. Corticosteroid psychosis (the symptoms including euphoria or feeling "high", delirium, insomnia, mood swings, personality changes and severe depression) may develop in people taking high dosages of steroids. The risk of developing cataracts, glaucoma or eye infections, especially viral

or fungal, is caused by long-term corticosteroid appliance. Symptoms of infections may be masked, because of immunosuppressive activity of these drugs. New infections may also occur during treatment (7). High-dose or long-term corticosteroid therapy may aggravate or worsen stomach ulcer, via blocking prostaglandines synthesis, which protect the mucous membrane of the digestive tract from toxic influene of gastric juice (11). Hirsutism and irregular menstruation may occur during treatment. Increased levels of red blood cells and excessive blod clotting is also caused by steroids (7).

Methotrexate is one of the folic acid antimetabolites (1). The most signifficant effects of its activity are revealed at the S stage of the cell growth cycle (7). It binds to folic acid reductase because of its similarity in chemical structure to folic acid, and thus hinders the production of tetrahydrofolic acid and its derivatives. Due to that, the synthesis of purine nucleotides is inhibited. Methotrexate is responsible for decreased activity of IL-1, IL-6 and also level of IL-2 receptor reduction (12). It leads to bone marrow depression (anemia, leucopenia, agranulocytosis, thrombocytopenia) and fertility disorders. Mucousities, ulcerations and bleeding of oral mucous membranes or other parts of gasrtointestinal tract, abdominal distress, nausea, vomiting, diarrhoea are also most common side effects. Methotrexate is widely distributed into body tissues. It does not appear to be appreciably metabolized. A part of its dose persists for weeks in organism, especially in the liver. It may lead to liver damage, hepatitis, portal fibrosis or hepatic cirrhosis (7). As it is excreted primarily by kidneys (90%), they are at particular risk (1). It is connected with precipitation of this agent, due to acid reaction. Renal impairment and insufficiency are caused by this drug. Pulmonary fibrosis, blurred vision, eye discomfort, and rashes, dermatitis, erythema multiforme, Stevens-Johnson syndrome may also occur during methotrexate treatment (12).

Another immunosuppressive agent is cyclophosphamide. Its activity is the most signifficant in the case of quickly proliferating cells. But, as an alkylating drug, cyclophosphamide may influence every stage of cell growth cycle (1). DNA, RNA, enzymes and hormones alkylation is caused by this drug. It also inhibits the synthesis of proteins and interferes with the growth of susceptible, rapiddly proliferating malignant cells. The mechanism is thought to be involved in cross-linking of tumor cell DNA. The main adverse reaction during cyclophosphamide treatment is leucopenia. 20% of patients complain of erosions, ulcerations and hair loss (7). These side effects are connected with the toxic influence upon epithelial tissues. Amenorrhea, azoospermia, sterility, ovarian fibrosis are also common. An increased risk of neoplasms and hemorrhagic cystitis should be considered. Cyclophosphamide is connected with the toxic effect of acrolein, the substance, which is metabolized into and which is excreted in urine. Therefore, it is necessary to take mesna as the way of prevention during the treatment (1).

The activity of B and T cells is inhibited by azathioprine. This drug is transformed in the organism into 6-thioinozynic acid, which replaces purine bases. Thus, the synthesis of DNA and RNA in antigen stimulated lymphocytes is disturbed (11). Azathioprine reveals alkylating activity and inactivates sulphydric groups (-SH). Protein biosynthesis, including immunoglobulines and hormones, is inhibited (7). Migration of macrophages and monocytes is blocked, therefore this drug reveals little anti-inflammatory effect (11). A toxic effect on dividing cells, especially in bone marrow, is present during azathioprine treatment. Thus, leucopenia, thrombocytopenia, macrocytic anemia (MCV, MCH growth) occur frequently. The loss of circulating leucocytes is used to assess azathioprine tollerance (12). In that case, folic acid is prescribed, the dosis of azathioprine is reduced or excepionally the medicine is discountinued (11). The next problem is liver disfunction, especially among patients with an existing defect of this organ (for example virus hepatitis). Therefore azathioprine administration should be stopped, because reduction in the dose does not prevent further damage (11). Hypersensitivity reactions, such as malaise, dizziness, anorexia, vomiting, rash, fever, chills, myalgia, arthralgia are frequent during treatment. Hair loss, arrythmia, decrease in arterial blood pressure, pancreatitis, colitis, diverticulitis, intestine perforation and digestive tract hemorrhages are rather rare (12).

Mechlorethamine – alkylating drug reveals good results in relation to rapidly dividing cells. Consequently, disorders of synthesis, disintegration or loss of DNA, RNA and protein function

may occur (12). This drug has numerous side effects, but myelotoxic activity is the most undesirable. Leucopenia (the most intensified on 6–8 day) and thrombocytopenia are not rare. Thorefore, if leucocyte level in blood decreases below 3000/mm^3 and thrombocyte level below 100000/mm^3 the drug administration is contraindicated. Gastrointestinal symptoms, diarrhoea, vomiting, nausea are common. Metallic taste, hair loss, fever, shivering, spermatogenesis disorders, irregular mentruation and infertility are also side effects. The serious problem is the induction of secondary neoplasms (leukemias, cancers) by mechlorethamine (12).

Cyclosporine A inhibits especially T cell activity. It acts by blocking reaction between antigen presenting cells (such as macrophages, Langerhans cells, T cells), and thus proliferation of helper lymphocyte and also synthesis and release of cytokines (IL-1, IL-2, IFNγ) is prevented (3). Cell receptors for IL-2 and macrophage activation are blocked by cyclosporine (7). It decreases inflammatory reaction by reduction of biosynthesis and secretion of IL-1, IL-6, IL-8, TNFα and TGFα (3). The mechanism of cyclosporine activity consists in direct suppression of genes and their products. This drug is bound with protein receptors called cyclophilines in cytoplasm of T cells and keratinocytes. Complexes, which inactivate enzyme stimulating different cells are formed. Thus, blocking of this specific enzyme, transcription of genes, including cytokine genes, is stopped (15). Cyclosporine probably induces production of TGFβ, which reveals immunosuppressive activity (11), stimulates fibrosis and directly vessel obliteration (15) and inhibits secretion of mast cell and gralulocyte granules, for example: proteases initiating inflammatory process (11). Cyclosporine is a very effective immunosuppressive drug. In dermatology it is prescribed for severe conditions, because of its ability to relieve symptoms. Unfortunately, it acts immediately and after treatment has been completed, relapse of disease is not rare (3). However, contrary to steroides, the aggravation of a disease, in comparison with the initial stage, is not observed during recurrence (3). Benefits and contraindications should be considered before administration of this drug. Monitoring of the function of organs, especially susceptible to damage, e.g. liver and kidney, is essential during cyclosporine therapy. Therefore, measurement of blood levels of creatine and blood pressure should be performed every two weeks. Additionally, blood cell count, levels of bilirubin, transaminases, uric acid and alkaline phosphatases should be monitored once a month (3). Because of immunosuppressive cyclosporine action, during a long-term treatment the neoplastic development must be considered (3). This agent does not inhibit the growth, therefore, it may be used for therapy in children (11). Moreover, it reveals slight toxic effects upon bone marrow (3). Kidney and liver toxicosis, high blood pressure, appetite loss, increased hair growth, gingival hypertrophy, tremors, lipid and carbohydrate metabolism disorders are the most common side effects. Paraesthesia, tingling in the hands or feet, diarrhoea, nausea or vomiting, headache, oedemas, irregular menstruation, anaemia are less common side effects (12). Hyperkalemia, hyperuricaemia, hypomagnesaemia (the result of renal tubule disfunction) (11) and hyperlipidemia (mostly hypertriglyceridemia) may occur during therapy (3). Cyclosporine is known to be toxic to the kidneys. Primary kidney function disturbances are rather functional and depend on cyclosporine dose. Due to afferent glomerular arterioles contraction, GFR is decreased. Therefore, blood levels of creatine and uric acid are elevated. During long term treatment the structural changes such as: tubule atrophy, hyaline arteriole degeneration and intestinal fibrosis are observed. The level of creatine is most important indication of renal efficiency. High blood pressure is not related to the dosage, but the length of treatment. Hypertension, occuring in the initial phase of therapy, detects hidden hypertension. When diagnosed at a further stage of the theraphy, it usually indicates renal and peripheral vessel constriction and kidney dysfunctions (3). Excessive hair growth is the result of increased receptor sensitivity to androgenes. The findings indicate, that brushing teeth at least three minutes after eating may prevent gingival hypertrophy (11).

Mycophenolate mofetil, a mycophenolic acid derivative diminishes proliferation of T and B lymphocytes and monocytes in inflammatory site. It is a selective, effective and reversible inhibitor of inosine monophosphate, which inhibits the pathway of guanosine nucleotide synthesis (12). It also inhibits synthesis of immunoglobulines and diminishes the production of cytokines:

IL-2, IL-4 and INF γ (1). Mycophenolate mofetil hinders synthesis of adhesive molecules on endothelial cells. It results in decreased inflow of the above mentioned cells into inflammatory site (11). Side effects of mycophenolate mofetil are associated with the suppression of DNA synthesis. It may contribute to leucopenia and sepsis. There is a higher risk of infections, especially of pulmonary or urinary systems and also dermis. Headache, dyspepsia are common. There are metabolic dysfunctions, such as hypercholesterolemia, hypophosphatemia, hypokalemia and oedemas. Anemia and thrombocytopenia are sometimes observed (12).

Immunosuppressive drugs, due to their high effectiveness, are applied in immune disorders in dermatology. Because of limited selective activity, these agents suppress the immune system. Therefore traditional immunosuppression is connected with serious side effects. Thanks to the development of new diagnostic methods, a lot of mechanisms, which play a role in the pathogenesis of diseases, have been explained during the last twelve years. These findings were used to describe indications and contraindications to apply immunosuppressive agents in many dermatologic disorders. Nowadays, some trials, whose purpose is to investigate the effectiveness of new immunosuppressive drugs, are carried out. According to them, tacrolimus (FK-506) seems to be a promising drug. The use of tacrolimus causes that kidney disfunction, hypertension (1), gingival hypertrophy and hirsutismus are relatively rarely (11). Unfortunatelly it is more toxic towards the nervous system and coronary vessels (11). It diminishes glucose tolerance and more often causes diarrhoea (1). Fresh hope seems to be: antilymphocyte serum, antithmocyte serum, monoclonal antibodies, CTLA-4- and CD28-molecules (11).

The diseases of connective tissues are the most common disorders. One of the main features of systemic lupus erythematosus is tissue and cell damage, caused by pathogenic autoantibodies and immune complexes. The etiology and pathogenesis are not completely known. Although LE shows some genetic predisposition, an environmental factors seems to be of special importance, as evidenced by association with UV-B radiation, sometimes UV-A, bacteria, viruses and occasionally medications. The essence of the disease is the dysfunction of the immune system and it results in increased generation of autoantibodies specific to LE. It is connected with hyperactivity of B lymphocytes, which produce specific autoantibodies, as well as with diminished function of T cells. The production of immunoglobuline tends to be higher, due to a defective function of gammaglobuline receptors, which are situated on macrophages and monocytes and complementary receptors on red blood cells. It make is impossible to remove complexes from the circulation. Therefore, they accumulate in tissues. There is a correlation between the activity of disease and TNFα (I and II type) soluble receptor level (6). The increase in their expression is connected with hyperactivity of cytokines (IFNγ and IL-2). Cyclophosphamide (it inhibits the production of antibodies), azathioprine (it diminishes the activity of lymphocytes) and steroides are administered as a routine therapy. The combination of steroides and cyclophosphamide in the patients with lupous nephritis, decreases the risk of developing renal insufficiency (6). According to Morton and Powell (1995-98) the findings referring to cyclosporine revealed that LE treatment may not be effective because of kidney damage developing during the disease (9).

Immunosuppressive drugs are prescribed for scleroderma treatment. This disease is characterized by inflammatory infiltrations and vessel alterations due to secondary fibrosis. Genetic, enviromental (silicon, aniline, tryptophan, viruses) and immunological factors are considered in the pathogenesis of scleroderma (6). Proper humoral and cell-mediated reactivities are disturbed. Damage to blood vessels leads to the accumulation of inflammatory cells (helper lymphocyte and monocytes) in perivascular space. These cells destroy the endothelium but on the other hand they stimulate the production of collagen and other proteins of extracellular matrix (3). Endothelium damage and fibrosis induction are caused by cytokines. Fibroblast and inflammatory cell proliferation is stimulated by proinflammatory IL-1 and TNFα. Due to these cytokines, the expression of ICAM-1 molecules on fibroblasts is increased and the contact between fibroblasts and lymphocytes is possible. IL-2 and its soluble receptor (sIL-2R) are factors used to estimate the severity of the disease (6). IL-2 activates cytotoxic, helper, B and natural killer (NK) cells and accelerates maturity of endothelium destroying cells (LAK). It also intensifies TGFβ synthesis in

monocytes and fibroblasts disorders. It stimulates the synthesis of extracellular matrix elements (collagen, fibronectine, preteoglicanes), inhibits the process of endothelium regeneration and dicreases the activity of some enzymes (for example collagenase) (8). Fibrosis induction is also caused by other cytokinins: IL-4, IL-6, IL-8 (6). Immunosuppressive drugs are prescribed in serious cases of scleroderma. Unfortunately, the effectiveness of these drugs is not high, therefore routine treatment with immunosuppressants in mild cases of diseases is not recommended. Scleroderma is treated with cyclophosphamide. In combination with steroids it is effective, especially in cases characterized by progressive lung or kidney fibrosis (6). Steroids are used for severe scleroderma, including lung fibrosis and pericarditis, particularly, if immunological factors distempers are observed. Steroids are very effective in the early stage of disease (6).

Apart from scleroderma and lupus erythematosus, immunosuppressive drugs are used for treatment of other connective tissue diseases, such as dermatomyositis or mixed connective tissue disease.

Psoriasis is a chronic, reccurent illness characterized by excessive and abnormal epidermal proliferation. Immunological factors play a role in complicated etiopathogenesis. Keratodermia is stimulated by TGFα and IFNγ (6). The increase of vessel permeability to inflammatory cells, penetration into dermis and activation of inflammatory condition are caused by intensive angiogenesis. Cell migration is connected with the expression of receptors for integrines on keratinocytes and the appearane of ELAM-1 and ICAM-1 molecules on endothelium. These processes ease the contact with lymphocytes. Cytokines produced by keratinocytes, such as: IL-1, IL-6, IL-8, TNFα and lymphocytes: IL-2 and IFNγ initiate the expression of macrophages (6). TGFβ is a common factor of vessel function, immune system and adhesive molecules and it leads to the dissemination of inflammatory process. IL-2 initiates new psoriatic lesions or causes the exacerbation of the existing ones. In the therapy of severe psoriatis, especially psoriasis arthropatica, methotrexate is very effective (6). In the treatment of severe, wide and recurrent psoriasis, in pustular psoriasis and psoriatic arthritis with tenderness and oedemas, cyclosporine is used (3,6). This drug inhibits the development of disease and helps to achieve remission (6). Small doses of cyclosporine and methotrexate applied at the same time, work synergistically, particularly in severe psoriasis arthopatica and psoriatic erythroderma (6). Mycophenolate mofetil, applied recently for the treatment of this disease, has been very promising. American and British studies proved that it may be active in less severe cases (5). Because of the lack of nephrotoxicity, it may replace cyclosporine if kidney dysfunction is observed (2).

Apart from that, immunosuppressive drugs are applied in blistering diseases. Pemphigus vulgaris is an autoimmune disease, in which development of blisters results from reducted epidermal intercellular adherence dysfunction, called acantholysis. It is a result of diminished function of molecules responsible for adhesion (6). The pathogenesis of pemphigus vulgarius, the most common type of pemphigus, is based on immunological reactions: Ig G-4 is the dominant immunoglobuline. The presence of these pathogenic antibodies is typical, found in the circulation as well as in the epidermis. The site of action in pemphigus vulgaris is the cadherine, the desmoglein III (130 kDa). It extends from the desmosomal plaque into the intercellular space and is known as the epidermal cell complex. The pemphigus antibodies are attached to the desmoglein and they activate acantholysis. These findings indicate that treatment should be continued under serological testing. The main aim of the therapy is remission, both in clinical conditions, and immune tests. The method of treatment should be individually tailored, accounting for age, disease activity and general condition. Systemic corticosteroids, due to their inhibiting effects upon immunoglobuline production are here widely used. They are recommended, especially in combination with cyclophosphamide. Other immunosuppressive agents (azathioprine, methotrexate) may also be helpful in the therapy, but their effectiveness is lower than cyclophosphamide (3). Cyclosporine combined with prednisolone in the treatment of pemphigus reduces the corticosteroid dose (3). Mycophenolate mofetil was found to be a relatively effective agent with very good response in pemphigus vulgaris (1999, USA). If the routine therapy is not effective (poor tollerance, side effects) mycophenolate mofetil treatment is considered (10). German rese-

archers reported on three patients with pemphigus vulgaris treated with mycophenolate mofetil as a single agent, and two as the combination with steroids. The follow-up period was 8–11 weeks. The study suggests that the effectiveness of mycophenolate mofetil is the same in both cases (4).

Bullosus pemphigoid is also one of blistering diseases. Contrary to pemphigus vulgaris, acantholysis is not present. Pemphigoid is characterized by autoantibodies reacting with components of the epidermal basement membrane, such as a 200kDa and 180 kDa proteins. These autoantibodies, belonging to IgG-4 do not activate the complement directly, but indirectly. Along with polynuclear leucocytes, the complement induces skin lesions. There is a number of eosinophiles, basophiles and mast cells in the inflammatory infiltrations. These cells reveal substances destroying basement membrane, due to degranulation. Because of a chronic course of the disease, the drugs are taken on daily basis. Patients are treated with medium doses of glucocorticosteroids (prednisone) during the exacerbation and small doses are applied during remission (6).

Because of multidirectional activity and the effectiveness of immunosuppressive drugs, they are used in the treatment of primary cutaneous lymphomas. Cutaneous lymphoma is a neoplasm of lymphocytes and therefore results in the proliferation of T and B cells at different stages of maturity. Among cutaneous lymphomas, about two thirds are derivatives from T cell (CTCL). CTCL includes mycosis fungoides (MF), Sezary syndrome (SS), large T cell lymphoma CD 30+, lymphoma of the subcutaneous tissue, angiocentric CTCL, CTCL CD8. (13). Mycosis fungoides account for 55–60% of all cutaneous lymphomas. Drugs and viruses are proclaimed the important factors causing the disease. At early stages, Th-1 cells are collected in the upper layers of dermis. They produce IFNγ, which stimulates the expression of ICAM-1 molecules on keratinocytes. It leads to epidermal changes. Clusters of neoplasmic cells are collected in the epidermis (Pautier microabscesses). Progression of the dissease (stadium tumorosum) changes the localization of infiltrations. At that time they are found in a deeper stratum of dermis. It is connected with increase of Th-2 cells, which produce IL-4. This cytokine lowers the level of IFNγ and IL-2. The consequense is decreased expression of ICAM-1 molecules and changes in T cell genes (3).Therefore, there is a necessity for a highly, effective drug. Mechlorethamine has been used to treat an early stage of mycosis fungoides for over 40 years. As an alkylating agent, it influences especially expansively proliferating cells. Response ranges vary from 50% to 75% in Th1 patients. However, therapeutic effect is accompanied by side effects (13). A similar but slow effect may be observed during chlorambucil therapy in Sezary syndrome. But in this kind of CTCL methotrexate is widely used. It acts as an antymetabolite of folic acid. It diminishes the production of biologically important molecules. This is a valuable, highly effective, treatment of choice. It is recommended, especially for early to intermediate stages of CTCL. According to Zaikheim, methotrexate was given in a low-dose therapy to 29 patients with erythrodermic CTCL. The researchers found that in twelve patients (41%) CR was observed and in five (17%) partial remmision took place. In two patients drug administration was discontinued, due to side effects. The median survival was 8.4 years (14).

Immunosupresive drugs are also applied in other dematological diseases resistant to routine therapy. In alopecia maligna a combination of cyclosporine A and steroids is recommended. Pulses of steroids and cyclosporine are also very effective in pyoderma gangrenosum (3, 6).

Therapeutic potential of immunosuppressive drugs is limited by dangerous side effects. Apart from inhibition of excessive immunological response to antigens and because of the lack of specific action, they result in total suppression of the immune system. That in turn produces a higher number of infections, an abnormal course of diseases and an increased risk of lymphomas and cancers. The sensitivity of serological and skin tests applied in diagnosis is also changed by immunosuppressants. Apart from that, a number of side effects typical of each drug should be considered. Therefore, the decision on applying any of these medications ought to be preceded by thorough analysis of the clinical history, indications and contraindications referring to each drug and potential toxicity and side effects.

REFERENCES

1. Danysz A.: Kompendium farmakologii i farmakoterapii, 47, 1998.
2. Davison S., Morris-Jones R.: Change of treatment from cyclosporin to mycophenolate mofetil in severe psoriasis. J-Dermatol., 405, 2000.
3. Gliński W.: Zastosowanie cyklosporyny A w leczeniu łuszczycy – wskazania, ograniczenia, dawkowanie i kontrola. Medipress, 7, 1999.
4. Grundmann-Kollmann M. et al.: Mycophenolate mofetil: a new therapeutic option in treatment of blistering autoimmune diseases. Dermatol., 957, 1999.
5. Grundmann-Kollmann M.: Treatment of chronic plague – stage psoriasis and psoriatic arthritis with mycophenolate mofetil. J. Am. Acad. Dermatol., 835, 2000.
6. Jabłońska S., Chorzelski T.: Choroby skóry, 193, 1994.
7. Kostowski W.: Farmakologia, 1077, 1998.
8. Majewski S., Szymańska E.: Pathogenesis of scleroderma. Medipress, 2, 1996.
9. Morton, Powell: An audit of cyclosporine for systemic lupus erythematosus and related overlap syndromes: limitations of its use. Annales of Rheumatic Diseases, 487, 2000.
10. Nousari A et al.: Mycophenolate mofetil in autoimmune and inflammatory skin disorders. Dermatol., 265, 1999.
11. Pączek S., Gaciąg Z.: Zastosowanie kliniczne nowych leków immunosupresyjnych. Klinika-Immunologia, 47, 1995.
12. Podlewski: Leki współczesnej terapii, 140, 1999.
13. Wąsik F.: Pierwotne chłoniaki skóry Współczesna klasyfikacja. Leczenie. Medipress Dermatologia, 3, 1998.
14. Zackheim H.S.: Cutaneous T cell Lymphoma: Update of treatment. Dermatol., 102, 1999.
15. Zembala M., Górski A.: Zarys immunologii klinicznej, 273, 1999.

SUMMARY

Immunosuppression consists in the breaking of different immune reactions. According to the mechanism of activity, these drugs reveal effects on each stage of the immune process. Among immunosuppressive drugs, steroids, antimetabolites, alkylating agents, cyclosporine, mycophenolate mofetil are used in dermatology. Therapeutic potential of these drugs is limited by dangerous side effects. Apart from inhibition the excessive immunological response to antigens and because of the lack of specific action, they result in total suppression of the immune system. That in turn produces a higher number of infections, an abnormal course of diseases and an increased risk of lymphomas and cancers. Therefore, the decision, on applying any of these immunosuppressive drugs ought to be preceded by thorough analysis of the clinical history, indications and contraindications referring to each drugs and potential toxicity and side effects.

Leki immunosupresyjne w dermatologii – korzyści i zagrożenia

Immunosupresja polega na hamowaniu odczynów immunologicznych na różnym etapie reakcji odpornościowej. Leki immunosupresyjne, w zależności od mechanizmu działania, wykazują nieco inny wpływ na poszczególne etapy procesu immunologicznego. W dermatologii zastosowanie znajdują m. in.: glikokortykoidy, antymetabolity, środki alkilujące, cyklosporyna A, mykofenolan mofetylu oraz takrolismus. Terapia oparta w dużej mierze na immunosupresji, mimo niewątpliwych korzyści, obarczona jest wieloma wadami. Cytostatyki, steroidy, poza znoszeniem nadmiernej odpowiedzi immunologicznej na konkretne antygeny, wskutek braku swoistości prowadzą do ogólnej supresji układu immunologicznego. Konsekwencją tego są częste zakażenia, odmienny przebieg kliniczny chorób, a także zwiększone ryzyko wystąpienia chło-

niaków i raków. Zmniejsza się również czułość stosowanych w diagnostyce testów skórnych i serologicznych. Dodatkowym zagrożeniem są liczne działania niepożądane, typowe dla danego preparatu. Dlatego decyzja o zastosowaniu immunosupresji powinna być poprzedzona wnikliwą analizą stanu klinicznego pacjenta, wskazań, przeciwwskazań odnośnie do konkretnego leku oraz potencjalnych efektów ubocznych.