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RESEARCH ARTICLE

IMMUNOSUPPRESSIVE EFFECTS OF PHARMACEUTICALS

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ABSTRACT

On the basis of published data and results of our own research, we are discussing classification, properties, side effects, indications, contraindications, principles of administration of antmetabolites, cytostatics, antlymphocytic serum and immunoglobulins, antibiotics, enzymes, corticosteroids and other hormones, salicylates, other pharmaceuticals, surgical methods, radiation in autoimmune treatment, malignant and other diseases.

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INTRODUCTION

In certain situations, it is necessary to calm the immune response with antigen-specific (immune tolerance) and antigen-nonspecific mechanisms, which may be induced actively using a specific antigen, allergen, hapten, as well as passively, by administration of specific or idiotype-bearing antibodies and by the use of influences non-specifically suppressing the immune system function in general. Additionally, there are situations where suppression of immune reactivity is a side effect of treatment of various diseases, complicating clinical condition of patients (D.K.Novikov and P.D.Novikov, 2009; Pokrovsky e*t al.,* 2012; Khaitov *et al.,* 2000; Briko and Pokrovsky, 2015).

Immonosuppressive therapy (IST) means the use of immunosuppresors and cytostatics for purposeful suppression of immune reaction in patients. Immunosuppressors are used in long-term low doses, they have pronounced anti-inflammatory effect and affect mainly RNA. Cytostatics are used in high concentrations, in short courses. They have low anti-inflammatory effect on their main target, the cell DNA.

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IST is used most extensively in oncology practice as antiproliferative agents in high doses, in transplantology - to suppress rejection of transplanted organs, for treatment of severe allergic and autoimmune diseases (Zemskov *et al.,* 2016, 2017). The above-mentioned drugs mainly target the macrophages, inductive and proliferative phases of immune response, etc., which is achieved through suppression of cell proliferation by blocking or destruction of nuclear DNA or RNA.

Additional details

Antimetabolites

They include purine antagonists — *6-mercaptopurine* (6-MP), *azathioprine*, pyrimidine antagonists — *5-fluorouracil, 5-bromodeoxyuridine* and folic acid antagonists — *aminopterin, methotrexate* with a structure similar to compounds of physiological importance (amino acids, nucleobases, vitamins) but lacking their properties. Getting involved in metabolism, they provide synthesis of compounds not assimilated by the cell and, which are blocking certain metabolic reactions.

Alkylating compounds

They include *cyclophosphan, chlorbutin, sarcolysine.* It is essential that in vitro efficiency of this drug group is not pronounced, as alkylation occurs after detachment of cyclic phosphorus-containing compound.

Table 1. Classification of immunosuppressive drugs (Kalinina *et al.*, 2008)

1."Major" immunosuppressors
1.1. Antimetabolites and nitrogenous base blocking agents
1.1.1. Antimetabolites and purine base blocking agents
1.1.2.Pyrimidine base synthesis blocking agents 1.1.3. Folic acid antimetabolites
1.2. Alkylating compounds
1.3. Antibiotics
1.4. Antilymphocytic and monoclonal antibodies
1.5. Analogues of endogenous immunosuppressors
1.6. Glucocorticoids
1.7.Drugs of various groups
2. "Minor" immunosuppressors
2.1. Derivatives of 4-aminoquinoline
2.2. Penicillamine
2.3. Gold preparations

In other words, immunosuppressive effect is provided not by the drugs themselves, but by the products of their degradation in vivo.

Antibiotics

Some of them, along with bactericidal and bacteriostatic effect on bacteria and fungi, have cytostatic and immunosuppressive properties. Their groups are differentiated according to their action mechanism. *Mitomycin C, dactinomycin, chloramphenicol, daunorubicin* are extensively used in clinical treatment.

Alkaloids

Colchicine, vinblastine, vincristine

Other drugs

For example, L-asparaginase, which is an enzyme produced by many organisms, e.g. by E. coli. It is used in treatment of autoimmune diseases and in transplantation. *Sulfazin, salazopyridazinum* belong to the group of sulfanilamides and, in recent years, are used in combination treatment of autoimmune diseases as immunosuppressive and anti-inflammatory agents. *Cyclosporine* is well proven. It is a fungal metabolite, a peptide composed of 11 amino acids, of a few varieties: A, B, C, F, D, H, etc., able to suppress T-cell immunity through suppression of T-lymphocytes without effect on B cells. *Procarbazine, D-penicillamine* are used in treatment of lymphogranulomatosis, leucosis, rheumatoid arthritis, scleroderma, pulmonary fibrosis. *Heparin and aminocaproic acid* have anticomplementary action suppressing complement-dependent reactions. They are used to treat autoimmune hemolytic anemias. If an antigen with high concentration of immunoglobulin G is injected, induction of immune paralysis is possible. Such enzymes as, for instance, *ribonuclease, deoxyribonuclease, xanthine oxidase* suppress formation of antibodies.

Hormones

It is established that pituitary hormone ACTH suppresses formation of γ-interferon; mineralocorticoids (*aldosterone*) have immunosuppressive properties, *parathormone* decreases colony-forming ability of lymphocytes and bone marrow cells. *Sex hormones, estrogens and androgens,* in high doses, inhibit mitoses, response to PHA, activation of NK and cytotoxic cells; chorionic gonadotropin, in low concentrations, suppresses antibody-producing lymphocytes.

As a whole, *adrenal hormones and sex steroids* are the sources of the inhibitory effect on the activity of immunocompetent cells.

Corticosteroids

This group of pharmaceuticals includes *pregnane derivatives*. Main targets of these drugs include induction of enzymatic activity, carbohydrate and amino acid metabolism. Other effects include stabilization of cell and lysosome membranes, inhibition of diffusion processes through biomembranes. Also noted are, increased intensity of catecholamine effect, inhibition of synthesis, release and effect of mediators in inflammatory processes and allergy. Presently, lymphocytes are categorized by their relation to hormones into cortico-sensitive and cortico-resistant population; the drugs can induce lymphopenia, monocytopenia, eosinopenia and accumulation of granulocytes.

Radiation treatment

Effect of radiation treatment is based on ionization caused by X-rays and γ-rays with formation of active radicals of water (HO_2+, H+, H_3O+) inside the cells. They cause alteration of nucleic exchange, which results in disorder of protein metabolism and cell function. High (lethal) radiation doses (900-1200 rads) completely exclude the possibility of any immune reaction. Sublethal doses (300-500 rads) suppress the capability of immune response for a long time. Mitoses and proliferation are suppressed in the lymphatic tissue right down to cell necrosis. After irradiation, the number of cells recovers slowly within 3 months, the number of CD19+ B lymphocytes - within 6 months only, and the number of CD3+ T-lymphocytes - within 12 months. In order to decrease side effects, extracorporeal irradiation, irradiation of the thoracic duct and transplanted material are used.

Antilymphocytic serum

Antilymphocytic serum, antilymphocytic immunoglobulin cause suppression of T-part of immunity. These drugs are obtained by heterologous immunization of large animals. Cells of spleen, lymphocytes of the thoracic duct, peripheral blood, lymph nodes are used as inducers. The drug is generally administered intramuscularly and intravenously in a dose of 5-10-20 mg/kg for 1-2 months, 1-3 times per week. Antilymphocytic serum and corticosteroids are synergic, so their combination is recommended. Indications for use include clinical transplantation of organs and tissues, autoimmune diseases (dermatomyositis, systemic lupus erythematosis (SLE), chronic hepatitis, multiple sclerosis, glomerulonephritis, myasthenia).

Surgical methods of treatment

They are used in autoimmune hemolytic anemia (*splenectomy*), sympathetic ophthalmia (*enucleation*), autoimmune pericarditis (*pericardectomy*), autoimmune thyroiditis (*thyroidectomy*), etc.

General indications for administration of immunosuppressors

These include confirmed diagnosis of *autoimmune disease* and its progression with poor prognosis. The situation where all other therapeutic possibilities have been exhausted, *resistance to glucocorticoids* and contraindications for their administration, for instance, *splenectomy*.

Also they include development of *life-threatening complications of autoimmune diseases* (hemorrhage, idiopathic thrombocytopenic purpura), *old age* (if possible).

Absolute indications

Transplantation of allogenic and xenogenic organs and tissues, *SLE, polyarteritis nodosa, scleroderma, Wegener's granulomatosis, malignant pemphigus, Goodpasture syndrome.*

Relative indications

They include immune *thrombocytopenia, immune hemolytic anemias, progressing chronic hepatitis, liver cirrhosis, rheumatoid arthritis, and membranous glomerulonephritis.*

Contraindications for administration of immunosuppressors

These are *infections* that can get out of control, forthcoming *major surgery*, for instance, kidney transplantation, *bone marrow insufficiency* wherein the cytostatic effect of immunosuppressors is very dangerous. The group of contraindications includes *decreased kidney and liver function, pregnancy* or an intention to beget a child, *severe disorders of the immune system.*

General side effects of immunosuppressors

- Bone marrow dysfunction. Primarily, cells with high mitotic activity (hematopoietic and sex cells) are damaged.
- Gastrointestinal tract disorders. Sickness, vomit, stomach disorders. Gastrointestinal hemorrhage is possible (methotrexate).
- Susceptibility to infections. Disorders are rooted in damage to skin and skin-mucosal barrier, suppression of lymphatic protective mechanisms (leukopenia, decreased phagocytosis activity, suppression of inflammatory processes), blockage of immune mechanisms. These events increase when combined with corticosteroids.
- Allergic reactions. They develop after intake of antilymphocytic serum and some other drugs. More often, they manifest as skin damage, eosinophilia and drug fever.
- Cancerogenic effect. Besides basic action, immunosuppressive drugs block mechanisms ensuring elimination of blast cells. Such cells, which have already passed through differentiation, are not controlled by the body and can be the reason for tumor formation. Especially often these processes occur in patients with “transplanted” tumors.
- Disorder of the reproductive function and teratogenic effects. When alkylating compounds are administered, there is a risk of infertility in both women and men in 10-70% of cases. When taking these drugs, pregnancy even 6 months after ceasing the treatment course is contraindicated.
- Growth retardation. Growth retardation may occur if the drugs are administered to children.
- Effect on the immune system. Cellular sensitization can be suppressed much easier than humoral one. Synthesis of IgG is more sensitive than synthesis of IgM. Mercaptopurine inhibits mainly T-dependent responses, cyclophosphan, azathioprine – B-dependent responses and T-cytotoxic suppressors. Corticosteroids have an equal effect on main populations of lymphocytes.
- Other side effects. Alkylating derivatives induce spermatogenesis disorder, amenorrhea, pulmonary fibrosis. Myelosanum — hyperpigmentation, loss of body weight. Cyclophosphamide — loss of hair, hemorrhagic cystitis. Antimetabolites — liver dysfunction. Vinca alkaloids — neurotoxic effect, ataxia, motor disorders.

Side effects of corticosteroids

They are numerous. (1) Obesity, cushingoid syndrome, growth retardation, negative nitrogen and calcium balance; (2) steroid diabetes, disorders of vitamin D metabolism; (3) decreased anti-infection resistance and bactericidal activity of leucocytes, aggravation of chronic infectious diseases (tuberculosis); (4) change of mood (excitements/depressions), psychosis; (5) hypothalamic-pituitary-adrenal axis suppression and decreased secretion or antagonistic effects of many hormones - insulin, growth hormone, calcitonin, luteinizing hormone; (6) disorders of the reproductive function with menstrual cycle disorder and malformations of the fetus during pregnancy; (7) suppression of the hypophyseal-adrenal system of the neonate; (8) rear subcapsular cataract, glaucoma; (9) peptic ulcer, gastrointestinal hemorrhage, pancreatitis, liver steatosis; (10) blood coagulation system disorders of, thrombembolia; (11) skin thinning, purpura, alopecia, myopathy, myocardiodystrophy, atrophy, pseudorheumatism, osteoporosis, destruction of vertebras, avascular necrosis, inhibition of skeletal maturation; (12) arterial hypertension, edemas, secondary immunodeficiency, decreased activity of antidiabetic, hypotensive, narcotic, anticoagulant, chemotherapeutic pharmaceuticals; (13) increased activity of bronchial spasmolytics, immunosuppressors, cardiac glycosides, indomethacin. Very important to note, that relatively long use of corticosteroids even in the dose of 2 mg causes formation of osteoporosis.

General principles of immunosuppressive therapy

- Treatment is started with high drug doses. As the desired result is obtained, the course is substituted with supporting course with 1/2-1/4 of the initial dose.
- Treatment efficiency is evaluated by the parameters and administration periods specific for each nosological entity: for immunosuppressive antibiotics, the period is 3 days, for enzymes and alkaloids – 10 days, alkylating derivatives – 10-14 days, cytostatics – 10-60 days. Generally, the duration of immunosuppressive therapy is at least 3 weeks, but there are possible exceptions from this rule, for instance, methotrexate should not be used longer than 4 weeks.
- If immune processes aggravate, drug doses should be increased.
- Almost all immunosuppressive agents are used in combination with hormones. In order to prevent side effects of the latter, hypotensive, diuretic, antibacterial drugs and potassium preparations are prescribed to patients. Taking into consideration the circadian rhythm of endogenous glucocorticosteroids, daily dose of

exogenous GCS should be administered in the morning hours, or 2/3 in the morning and 1/3 in the afternoon. Intermittent administration is possible, which means that two-days drug dose is given in a single intake every other day.

- Withdrawal syndrome. Corticosteroids may be stopped immediately after a short 5-10 days cycle. If duration of treatment lasted a few weeks or months, this should be done gradually, with stepwise decrease of hormones intake by 25-50% per day during few days. Further decrease should be slower, by 2.5mg of the drug each 2-3 days.
- Immunosuppressors are divided into three groups, depending on the nature of their action. *First group* – drugs suppressing immune responses are used just prior to the injection of antigen (*myelosanum, corticosteroids, mitomycin C, procarbazine*), *second group* – drugs effective in 1-2 days after the injection of antigen (*antagonists of purine, pyrimidin, folic acid; vinca alkaloids, actinomycin*), *third group* – drugs active both before and after the injection of antigens (*cyclophosphan, antilymphocytic serum, procarbazine, mustard derivatives, mitoclomine and its analogues, ionizing radiation*).
- Alternative immunotherapy – simultaneous or sequential use of immunosuppressors and immunostimulants in patients with 2-3 degree stimulation of 3-4 immune status parameters; with high titers of autoantibodies against antigens of internal organs; existence of diagnosed autoimmune diseases (Zemskov *et al.,* 2016, 2017). Effective combinations are composition of cyclophosphan, corticosteroids, radiation, antibiotics with sodium nucleinate, derinat, isoprinosine, thymomimetics (imunofan, tactivin, thymogen), myelopid, cycloferon, galavit, superlymph.

Immunosuppressive effects of antibiotics

A great number of experimental works and clinical observations reveal a presence of immunosuppressive effect even in short-term courses of such antibiotics as penicillin, streptomycin, tetracyclines, antituberculous and antifungal drugs (Khaitov and Ataullakhanov, 2012; Pokrovsky *et al.,* 2013; Zemskov *et al.,* 2007, 2013). Most frequent effects of antibiotics are: (1) defects of primary immune response formation, differentiation of stem cells caused by levomycetin, rifampicin, doxycycline; (2) decreased postvaccinal immunity against bacteria and viruses caused by levomycetin, cephalosporins and decreased anti-infectious resistance against flu virus, pityriasis rosea, pityriasis versicolor, etc. caused by aminoglycosides, penicillins, cephalosporins; (3) suppression of cytotoxic activity of T-lymphocytes by amphotericin B, tetracycline, doxycycline, monocycline, limecycline, cephalothin, levomycetin; (4) inhibition of chemotaxis, opsonization, bactericidal activity of phagocytes by cephalosporins, aminoglycosides, tetracycline, erythromycin, tobramycin, amikacin, doxycycline, limecycline, rifampicin, amphotericin B; (5) suppression of formation of immune memory cells, activity of complement, lysozyme, β-lysines, bactericidal properties of blood serum caused by ampicillin and formation of post-operational infectious complications with the use of neomycin, oleandomycin, synthomycin, streptomycin (Zemskov *et al.,* 2007, 2016).

Main pharmaceuticals for treatment of tuberculosis: kanamycin, streptomycin, in a lesser degree rifampin, isoniazid, pyrazinamide, ethionamide, especially combination of isoniazid+rifampicin+streptomycin and isoniazid + rifampicin+kanamycin, in long-term use, suppress immune response to thymic-dependent and thymic-independent antigens, delayed type hypersensitivity, indicators of nonspecific protection of the body (Briko *et al.,* 2013; Yushuk *et al.,* 2014). Today, *polymyxin, levomycetin, vibramycin* may be excluded from the clinical use almost completely, despite the encountered sensitivity of causative agents of purulent-septic complications to these antibacterial drugs, as these drugs suppress phagocytosis and complicate the course of purulent-septic processes. However, the use of these drugs with specialized immunomodulators decreases significantly the lethality in general purulent infections (Zemskov *et al.,* 2015).

Immunosuppressive effects of other pharmaceuticals

Active immunosuppressors are *reserpine, benzedrine, furagin, furacilin, phenibutum, valproate sodium* and other psychotropic drugs. *Antihistamine drugs inhibit natural anti-infectious resistance, immunity,* incl. vaccinal immunity, they *"erase" the immune memory. Amidopyrine, indometacin, salicylates* suppress *AG-AT response*, which means that each time as these antibodies are required for protection (diphtheria, toxicosis, etc.) this reaction is unsustainable. *Sulfamethoxazole, bactrim, nitrofurantoin inhibit formation of antibodies, functional activity of lymphocytes*. *Paracetamol and indometacin decrease indicators of phagocytic activity of* peripheral *neutrophils, immediate and delayed type hypersensitivity*. *Salicylates, nonsteroidal anti-inflammatory drugs* in long-term use in therapeutic doses suppress immune reactivity of the body, which is the reason for being called "minor immunosuppressors". It is known that they *suppress formation of antibodies* against various viruses, bacteria and their toxins, heterologous proteins and erythrocytes, *migration of T and B lymphocytes, disturb cooperative interactions of immunocytes and inhibit development of cell-mediated immune reactions, contribute to the development of* drug-induced secondary *immunodeficiency* (Borisov, 2005). When drugs are combined, immunotropic effects change: when antibiotics and antihistamines are combined, suppression is summarized; brufen inhibits stimulating effects of thymomimetics, polysaccharides potentiate the effect of myelopeptides, sodium nucleinate corrects side effects of corticosteroids and broad spectrum antibiotics.

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