

Principles for the Purpose of Immunotherapy

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Abstract

Based on the consequences of the implementation of the fourth factor in the development of diseases - immune disorders, the indications and principles for prescribing immunotherapy, the interpretation of immunograms are discussed. Variants of immunotherapy, mono- and combined immunotherapy are covered in detail. The problem of various types of immunocorrection, immunometabolic, non-drug, complex and alternative immunotherapy is discussed in no less detail.

Keywords: immunotherapy, types and principles of immunotherapy, interpretation of immunograms

Introduction

The strategy for the development of medicine has led to the understanding that almost any pathology is the cause or consequence of immune disorders that contribute to the chronicity of the underlying disease and its complications. This situation requires the use of immunologically active drugs, without which a quick and complete cure of patients is often difficult. However, the list of such drugs is enough is limited and diverse, and the awareness of clinicians about the principles of immunotherapy is clearly insufficient. This situation often leads to the arbitrary prescription of immunotropic drugs with a questionable clinical outcome. This is confirmed by the fact that the correct use of one immunotrope in some cases is completely insufficient and two or even three drugs are required when corticosteroids, antibiotics, cytostatics and other drugs with immunosuppressive properties are prescribed to patients with multidirectional immune changes. This makes it clear how dangerous the lack of information about the immune properties of many drugs that are not yet related to immunotropes. It is easy to see what unwanted surprises await the uninformed clinician.

The general rationale for the importance of clinical immunology in recent years is the establishment of the fourth factor in the development of diseases - immune disorders, which are

based on excessively weak or excessively strong immune responses, which is clinically expressed by immunodeficiencies or hypersensitivity with specific manifestations of allergies and autoimmune pathology ^[1,2]. It is reported ^[3] that the frequency of their occurrence in the general population of immunocompromised people reaches 40-80%. This led to: (1) - a sharp increase in the frequency of infectious diseases in general, purulent-inflammatory diseases, in particular, with an erased altered clinical picture, chronic course, complex etiology caused by the association of opportunistic pathogens with intracellular parasites that cause immune deficiency ^[4]. (2) - the accumulation of persons suffering from various somatic diseases with immunopathological genesis (bronchial asthma, rheumatism, allergic vasculitis, etc.), the effectiveness of whose treatment is often insufficient ^[5,6]. (3) – the formation among the population of a significant stratum of people with various types of drug, food, other intolerance, autoimmune pathology, with a high risk of developing malignant neoplasms, vaccination reactions, infertility, etc. ^[7,8]. All this has led to the widespread use in practical medicine of immunotropic drugs, in knowledge of which there are still certain gaps. That is why there is a need to understand in detail the principles of immunotherapy, which is the subject of this article.

Immunotherapy

This is the appointment of pharmacological/non-drug interventions to compromised contingents to correct immune disorders and achieve a therapeutic effect. Immunotherapy is carried out for the treatment of diseases with increased reactivity (allergic, autoimmune), primary and secondary immunodeficiencies, tumors and lymphoproliferative processes, post-transplant reactions, reproductive disorders. According to the nature of the action, immunotherapy is divided into stimulating, suppressive, specific, nonspecific, auxiliary, preliminary and metabolic. According to the mechanism of action, respectively, on the active (antigens, vaccines) and passive (immunoglobulin antibodies) ^[4,5,9].

Indications and principles for prescribing immunotherapy

Indications for immunotherapy

Realized: (1) with immune deficiency, especially with a decrease in infectious resistance, which manifests itself in unusual frequent, severe, prolonged and complicated infections with uncharacteristic etiology; (2) premature loss of teeth, unexplained bronchiectasis, poor wound healing, deterioration in general well-being, chronic diarrhea, hemolytic disorders, metabolic diseases, malnutrition, malignancy, aggressive long-term treatment; (3) in allergic diseases in cases of their complications of secondary immune deficiency, manifested in the aggravation of atopic dermatitis with pyoderma, bronchial asthma with chronic purulent-inflammatory bronchitis, etc.; (4) in autoimmune diseases, when patients are prescribed immunosuppressors and/or stimulants of the suppressor link of immune reactivity; (5) in acute pathological, especially infectious processes, immunotherapy should be short within a few days or a week, in chronic ones longer, first with daily, and later with intermittent administration of drugs; (6) in the treatment of infections, immunotherapy is combined from the first day with antibiotics, antifungal, antiprotozoal or antiviral and other etiotropic drugs; (7) monoimmunotherapy is used for rehabilitation activities and incomplete recovery ^[4,8,10].

Principles of prescribing immunotherapy

A decrease in the value of any immune parameter in a practically healthy person is not a basis for immunocorrection. The high adaptive capacity of the immune system, its multicomponent nature and multilevel organization make it difficult to change its functions in a direction with a sufficiently high risk of inducing immune responses. Therefore, the implementation of the properties of immunotropic drugs is never linear, it depends on the disease, the nature and degree of the immune system disorder, the stage, phase of the pathological process, and many other reasons. With this in mind, we have developed a series the principles of prescribing immunomodulating agents, in which immunotherapy is based on (1) traditional clinical and laboratory diagnosis of diseases in a patient; (2) determining (diagnosing) the nature of immune disorders in a particular patient; (3) its coincidence with the targets of the action prospective corrector; (4) in the presence of data on the effectiveness of the proposed corrector in this pathology. Moreover, it is necessary to distinguish between the actual diseases of the immune system, in which changes in reactivity are stable, pathogenetic, requiring correction, and compensated temporary disorders of the immune system, more precisely, immunopathological reactions as a result of various causes that do not require specific treatment. ^[2, 10, 11].

Methodology for the interpretation of immunograms and the appointment of immunocorrection

To implement this cluster of work, it is necessary to have survey data from an adequate comparison group (norm) of healthy people of the same age and gender without acute and chronic diseases, determine the severity of laboratory disorders and display the nature of the pathology in the patient in the form of a formula for disorders of the immune system FDIS $[(I_s/I_h - 1) \times 100\%$, where R_b , I_h - immune indicators of a sick and healthy person] and a preliminary determination of the response of patients to certain immune effects ^[12]. It is extremely important that the following must be taken into account: (1) the dependence of changes in immune parameters on the age of patients, biological rhythms, the presence of diseases, especially chronic and other factors; (2) genetic blood markers in patients (antigens of the ABO system, Rh factor, haptoglobins, etc.); (3) immunotropic, allergic the effects of traditional drugs, non-drug therapeutic and diagnostic effects and their combinations; (4) metabolic and side effects of immunomodulators; (5) maintaining the profile and effects of immunomodulators in various diseases and in the presence of the same type of immune disorders; (6) influence on the nature and spectrum of action of immunocorrectors of initial immune disorders in patients; (7) implementation of the immunocorrector effect depending on the frequency of administration, stage, localization of the process, inflammation features, combination of diseases, allergization, etc.; (8) influence on the severity and mechanisms of action of immunomodulators of ongoing basic treatment, other immunotropes, vaccines, serum preparations; (9) preservation of the action spectrum of immunomodulators in patients with repeated introduction and with an increase in the severity of the immunotropic effect; (10) connectedness of the links of immunity, when the elimination of the deficiency of one parameter leads to the activation of another; (11) nucleic acid metabolism disorders, accumulation of excess body weight and other metabolic disorders in patients; (12) features of the use of immunotherapy in geriatric practice.

It is essential that preference is given to passive therapy, while with active therapy it is necessary to increase single, course dosages, the frequency and duration of administration. Moreover, it is desirable to use preparations of nucleic, synthetic origin, combined, complex, immuno-metabolic correction. Standard doses of administered drugs must be changed depending on the age of the patients and the nature of the pathological process. For example, drugs thymus young patients can be used on a reduced schedule (only 2-3 injections). Whereas for elderly patients, therapy should be carried out according to the type of replacement, and preferably in long courses up to 10 injections or more, however, with the final injections, it is necessary to use 1/2-1/4 doses of thymomimetic and with longer intervals to exclude the "withdrawal" symptom. Under certain conditions, for example, if the patient has liver damage, gastroenterocolitis, drug allergies, it is desirable to prescribe immunomodulators of plant origin. In this case, the dose of drugs can be reduced to homeopathic, and the course can be extended to 1-3 months. This approach is also justified in children's practice.

Requirements for immunomodulators

These include the known biochemical composition and its reproducibility in production, minimal activity in the absence of side, teratogenic and other effects. Mandatory requirements include areactogenicity and easy biodegradation in the absence of cumulative effect. Compatibility with other drugs, a preferred immunomodulatory effect, natural origin and oral administration are also required [5, 9,13,14].

Types and options for immunotherapy

Numerous types of immunotherapy include: (1) specific (antigenic) active stimulatory or suppressive; (2) specific adaptive (transfer factor); (3) specific passive substitution (antibodies, immunoglobulins); (4) specific passive suppressor (antibodies); (5) non-specific active stimulatory (adjuvants, mitogens, modulators) and suppressor (mediators, immunoglobulins); (6) non-specific adaptive stimulatory (thymo- and melopeptides); (7) non-specific passive substitution (antibodies, immunocompetent cells) and suppressor (glucocorticosteroids, immunosuppressants, cytostatics, antimediators); (8) systemic, regional, systemic-regional, metabolic, immuno-metabolic, mono- and combined, alternative, complex, adjuvant active and passive, non-drug, pharmaco-non-drug, anti-infectious, preliminary, auxilliary [2,8,15,16, 17].

Immunotherapy options

Auxilliary immunotherapy

It is used to eliminate indirect causes of the development of immune disorders, such as intestinal disorders, namely intestinal dysbacteriosis and enzymatic disorders, increased emotionality, excessive activation of neurovascular reactions, diseases of the liver, endocrine system and metabolic disorders, etc.

For example, the elimination of intestinal disorders is carried out with the help of bacteriophages, pre-, pro-and synbiotics. For the correction of enzyme deficiency, festal, engistal are used, to stimulate the separation of bile, true choleric, for example, allochol, synthetic (tsikvalon), vegetable (immortelle), hydrocholeric (mineral water), cholekinetics (magnesium sulfate), antispasmodics (no-shpa). For the treatment of neuroregulatory disorders, adaptogens (Chinese

magnolia vine), sedatives (hawthorn fruits), vitamins (C, E, A, B), trace elements (zinc, cobalt, selenium), active food additives, hepatoprotectors are used for metabolic disorders.

Replacement immunotherapy

It consists in the introduction of metabolic immunoactive factors in case of their insufficiency in patients. For example, in patients with dysnucleotidosis, i.e. ribonucleotide deficiency, which develops with gastric ulcer, duodenal ulcer, ulcerative colitis, periodontal disease, dystrophic skin ulcers, pigmentary retinal dystrophy, etc. the introduction of native and synthetic low- and high-molecular nucleic drugs (sodium nucleinate, ridostin, derinat, polyinosine, synthetic polynucleotides) ^[18]. With a deficiency of immune globulins in conditions of primary and secondary immunodeficiencies, severe infectious diseases and in other cases, serum preparations are used (immunoglobulins, in the family of which include gabriglobin, octagam, immunovenin, pentaglobin, etc., blood plasma, complex immune preparation (CIP), etc.) ^[19].

Monoimmunotherapy

This term is understood as the appointment of a single immunomodulator in the general complex of drugs to the patient.^[10] Moreover, the indications for the use of monoimmunocorrection are the presence of a patient with immunodeficiency of 2–3 degrees in one indicator or 1–2 degrees in 3–5 parameters at the same time, severe comorbidities, including allergic, autoimmune diseases, malnutrition, obesity, and advanced age. These include atypical temperature reactions, i.e., a tendency to prolonged subfebrile condition, excessively strong, weak or no febrile reaction in acute infectious diseases and unsuccessful traditional treatment for a month.

Features of the implementation of the effect of monoimmunocorrection

They consist in the fact that: (1) The effect of mono-influences depends to a greater extent on the characteristics of the initial immune disorders than on the used variant of immunocorrection. (2) A certain influence on the nature and effectiveness of modulation is exerted by the scheme of application and, to some extent, the dose of drugs. (3) In the spectrum of action of immunomodulators, cellular rather than humoral defense mechanisms are more often represented, and the effect on nonspecific factors was minimal. (4) The action of immunotropic agents was modulating, causing stimulation of decreased and suppression of overestimated values of parameters, the first effect being dominant. (5) The direction of the resulting effect of the same immunotropic agents in a number of cases was alternative. (6) The effectiveness of immunocorrection with individual preparations was somewhat greater for more severe than for mild pathological processes. (7) In general, the significance of eliminating immune disorders when using sodium nucleinate and thymic preparations thymoptin, thymogen and tactivin was more pronounced than with other immunomodulators. (8) Comparative efficacy of various immunotropic drugs of thymic origin showed their certain similarity, both in terms of the mechanism of action and the severity of effects.

Combined immunotherapy

Such therapy is understood as an additional simultaneous or sequential administration of immunomodulators of various origins and mechanisms of action to patients ^[20]. Indications for such effects are: (a) chronic course (more than 3 months) of the main pathological process, its frequent relapses, concomitant complications, secondary diseases; (b) severe intoxication syndrome, metabolic disorders, loss of protein by the kidneys or other routes, helminthic invasion; (c) unsuccessful immunocorrective therapy with a single drug for a month; (d) a high degree, often the third, of immunodeficiency or a combined lesion of T- and B-links of immunity; (e) multidirectional disorders of the immune system, consisting in the stimulation of some and the suppression of other indicators relative to the norm.

When evaluating the effectiveness of combined differentiated immunocorrection, a number of features were found. In this aspect, there is a certain stereotype of the reaction of the immune system, little dependent on the type of immunotropic effect, as, for example, in diphtheria and erysipelas, when the same immunomodulators in the first case cause an effect on B-, in the second on T-dependent reactions. In general, with rare exceptions, the effectiveness of combined immunotherapy is higher than when using mono drugs. In this case, the immune and clinical orientation, as a rule, coincide.

With a combination of target drugs, their actions may be preserved or changed. The same remedies in various pathological processes and differentiated combinations can be neutral, realize dominant or minor potencies.

With the combined use of immunotropic drugs, the vector of parameter changes may change, the activity of individual components of the joint effect may increase or decrease. It seems that the dependence of the nature and effectiveness of combined immunocorrection on the initial level of immune disorders in specific diseases, in contrast to mono-influences, is somewhat weakened and is largely determined by the qualities of the selected drugs ^[9].

Alternative immunotherapy

It is understood as the simultaneous appointment of immunosuppressive and immunostimulating agents to the patient. Indications for the use of alternative immunocorrection are the presence of a pronounced stimulation of the second or third degree at the same time 3-4 parameters of the immune status, high titers of autoantibodies against antigens of internal organs and the presence of autoimmune diseases.

Features of alternative immunocorrection are that (a) the resulting effectiveness of immunotropic interventions depends on the properties of the sum of immunostimulants and immunosuppressors included in the combination; (b) the effectiveness of a combination of several pharmacological immunomodulators in comparison with the use of monodrugs against the background of immunosuppressive therapy does not give a clear advantage; (c) the nature of the target action of pharmacological drugs may vary depending not only on the passport activity of the drug and the type of pathology, but also on the very fact that patients receive corticosteroids or cytostatics; (d) the immunocorrective effect of sodium nucleinate is somewhat more pronounced than that of other drugs of different origin and mechanism of action; (e) character the immunotropic action of immunomodulators is more pronounced and shows its specificity mainly in the early stages after

treatment. After massive immunosuppressive therapy, several months, these features disappear, being replaced by a typical reaction of the immune system, little dependent on the type of immunotropic exposure; (f) in severe chronic diseases, such as polyetiologic liver cirrhosis, multiple sclerosis, etc., the peculiarities of the implementation of the effect of various drugs are lost and the dependence on the type of pathology and its experience is eliminated, which are so significant in the case of the use of modulators without immunosuppressive effects; (g) direction of action, i.e. the vector of immunotropic drugs from the initial level can be both stimulating and suppressive ^[9,20].

Complex (multicomponent) immunotherapy

This refers to the simultaneous appointment to the patient of more than two types of immunotropic effects of pharmacological, non-drug, vaccine, serum, metabolic/ antioxidant.

Other methods of immunotherapy

This information is presented in our communications ^[3a, 9,10b;12, 21].

Active adjuvant immunotherapy

Represents the simultaneous appointment of vaccines, toxoids, other antigenic preparations with immunomodulators and adjuvants to patients.

Passive adjuvant immunotherapy

It consists in the simultaneous administration of serum immunoglobulin preparations with immunomodulators and adjuvants to patients.

Immuno-metabolic immunotherapy

With it, a combination of immunomodulators with metabolic agents and antioxidants is realized, which include hypoxen, CigaPan, lemontar, wobenzym, preventan, etc.

Pharmaco-non-drug immunotherapy

Represents a combination of pharmacological immunotropic drugs and non-drug factors, which include low-intensity laser radiation, plasmapheresis, sorption, ozonized solutions ^[22].

Systemic regional immunotherapy

It is used in conditions of simultaneous appointment of immunomodulators of general and local immunity to patients.

Anti-infective immunotherapy

Used in combination of pharmaceutical antibacterial and bactericidal drugs, bacteriophages with immunomodulators.

Comprehensive sequential immunotherapy

It is performed in those cases when, against the background of metabolic cocktails, the introduction of two or three immunocorrectors of various origin and mechanism of action is implemented with an interval of two to three weeks.

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None declared

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