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Tactic- and Strategy-affiliated Policy to Drive Clinical Immunology Ahead and to Secure the Future

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Abbreviations: BA: Bronchial Asthma; COPD: Chronic Obstructive Pulmonary Disease; DP: Deep Pyoderma; CD: Clusters of Cellu-Lar Differentiation; Spnbtrt: Spontaneous Nitro Blue Tetrazolium Reduction Test; Actnbt: Activated NBTRT; TNF: Tumor Necrosis Factor; SC: Tab Cells; TSH: Thyrotropine; IL: Interleukins; E: Eosinophyls; ISDF: Immune System Disturbances Formula; ICTF: Immune Corrections Targets Formula; CNS; Central Nervous System; CIC: Circulating Immune Complex; Ig: Immunoglobulins; Pars: Pseudoallergic Reactions; LDL: Low-Density Lipopro-Teins; VLDL: Very Low-Density Lipoproteins; NK-Cells: Natural Killer Cells; HT: Hashimoto's Thyreoiditis; Hbs Anti-Gen: Hepatitis B Surface Antigen; RNA: Ribonucleic Acid; ABO System: Genetic System of Blood; Camp\ Cgmp: Adenosine Monophosphate Cyclo\Guanosine Monophosphate Cyclo; ACTH: Adrenocorticotropic Hormone

Introduction

The progressive increasing of amount of immunocompromised persons with misdirected defence reactions is registers recently. This phenomenon is based on several factors, such as negative environmental factors, food intake changes, increasing of pharmacological loads on patients, aggressive diagnostics and treatment technologies etc. By today's understandings, the immune system is a critical target for these effects. Donozological changes, which are initially developed, later become factors that induce and aggravate state of the disease [1,2].

Individual field of medicine, called clinical immunology, was created to solve these noticed problems. The modern its definition as a field of medicine involves pathogenesis, diagnostics, treatment and disease prevention studies, which a based on disturbances in immune reactivity. Many causes, such as anatomic features of immune system, functional complexity, chance of restoring homeostasis by the various pathways, controversial methodological evaluation of its disorders, absence of distinct ideology of modulation approaches and others do not allow include clinical immunology in a field of evidence based medicine.

It is commonly believed that immune system develops standard deterministic reactions on pathological processes, which a priory recognized as the constant. However, in reality cases with multidirectional dynamics of immune sys-tem components are appeared in humans with specific diseases.

A strong fixedness of immune system targets, which are modulated by pharmaceuticals, is does not prove out by practice but, on the contrary, the changes of application points and action vector of the same medications at various diseases and also at different patients are observed [3,4].

The fact that immune system takes an exceptional position in the organism is consists in its functioning, which associated with nervous, endocrine, excretory and others systems, which also regulate the immune system. This makes understanding and interpretation of strength of preparations, which act on defense reactions, and creating of targeted correction conception more difficult. Consequently, effectiveness of immunotherapy in some cases is unexpressed. It promotes to reducing an interest of practicing physicians to clinical immunology as a medical discipline that bar its development.

Solution of a number of tactical and strategic objectives is necessary for creation of ideology of adequate assessment and targeted correction of immune disturbances. We on the basis of big clinical material and experience have developed 6 provisions which we apply in clinical immunology:

- Qualified planning and objective interpretation of clinical laboratory monitoring of patients, adequate mathematical data processing.
- Reproduction of natural evolutionary developed mechanisms of disturbed immune homeostasis repairing.
- Knowledge of the influence of the clinical diseases characteristics (pathogenesis, stage, localization, sensibilization etc.) on immunologic response modificators activity.
- Account of targets drift when some immunotropic medicines are combined relative to individual impacts.
- Usage of complex multicomponent modulating therapy for controlled correction of immune disturb-ances at pathological processes with complex pathogenesis.
- Incompleteness of planning and interpretation of laboratory diagnostics results of immune disturbances.

Incompleteness of Immune Disorders Laboratory Diagnostics Results Planning and Interpretation

Pre-randomization of patients in terms of main clinical laboratory parameters, representativeness of sample definition, standardization of methods and time limits of laboratory monitoring and treatment

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are necessary for receiving of objective information in planning of observations.

Phenomena of norm and pathology in medicine, particularly in immunology, have an essential importance. Parameters of immune system of a healthy person and patient (for example, after antigenic stimuli they are equal in digital measurement, but functionally they are differential) are expressed the ability of the organism to resist against repeated administration of foreign agents. There are also regularities after administering of immunoamplifiers or immunosuppressors to patients.

The formation of control groups is also determines effectiveness of immunopathology identification. Among this healthy persons only occurrence once donors with must be included. These donors are also must be randomized by gender, age and other factors as test persons. It puts on an agenda the presence of standard indicators in most laboratories. In the long view, not only factors, such as age and sex, but ones, such as circadian biorhythms, geographical location, state of geomagnetic field, ecological features and others will be needed to assess the effect on the immune status [5,6].

The identification of main populations and subsets of lymphocytes, based on receptors detection by different methods, has difficulties with rendering of function of cells, which have various markers, and absence of due standardization of systematic approaches for these cells identifying.

Assessment of immunoglobulins sets and subsets in serum is also undetermined, because of protein concentration as a minimum consists of antibodies synthesis against antigenic inductor, myogenic action of gut microflora and detoxication function of liver. For example, the hyperglobulinemia may be due not to the features of patient immune reactivity, but clinically inert cholangitis and cholecystitis.

However, the characteristic of phagocytes absorption capacity and metabolic activity of cytokines, adhesines and all above mentioned signatures, which are nonspecific and depend on such factors as anti-infective resistance, cur-rent treatment, blood pH etc.

The paradox of clinical immunology is also that concrete reactions are estimated by nonspecific methods. For example, a share of specific antibodies in a general population of serum globulins is not more than 1%.

Certain difficulties in determining of relative or absolute amount of lymphocytes sets and subsets do exist. This is due to ignoring of circulating blood volume, which can fundamentally change indicator values at the time of administration of plasma-substituting solutions, fluid loss by patients, leukocytic reaction and other.

The interpretation of immunograms changes in the course of treatment is also quite difficult and ambiguous. For instance, in the presence of inflammatory process the amount of circulating T-lymphocytes may decrease because of migration of these cells into abnormal focus. In this case the deficiency of blood cells comparative with markers values in healhy volunteers is physiological phenomenon.

The disorders of the immune function of any level in vitro are not necessarily indicate that the damage is localized here. For example, the dysleukopoiesis in the bone marrow may be related with panmyelophthisis, synthesis of autoantibodies against progenitor cells, disturbance of regulatoty interactions between T-lymphocytes and macrophages and others mechanisms.

Thymus inherited and acquired defects induce inadequate T-cells aging, decreasing of intensity of cellular and secondary humoral reactions. The disturbance of antigen-presenting function in macrophages, HLA-antigens absence at the lymphocytes surface, formation of immune tolerance because of specific suppressor's activation, immune paralysis and others may also cause the immunodeficiency.

Detecting of any immune defect in in vitro assay is optionally suggests availability of this defect in organism and conversely. For example, low antibodies level may depend on their joining with microbes and high level may detecting in cases of disseminated process and in convalescence. In this case the humoral factor even at high concentration does not effect on intracellular parasites and antibacterial antibodies do not neutralize bacterial toxins etc.

Medicinal preparations act on expression of immune disorders by influence on leuko and lymphopoesis. This is manifested in typical variations of leucograms during inflammation and in natural history of immune figures during diseases development [7].

These facts leaded to formulation of fundamental diagnosis rule of immune disturbances. This rule lie in the fact that the presence in examined patient not only typical changes of immunological status but relevant clinical signs (syndromes) of immune disease.

When revealing of immune homeostasis common patterns usually the average values of laboratory data in patients. But these values may conflict with individual characteristics of individual patients. The approach of immune response accuracy was developed by Petrov and lies in the fact that immune response determined by immune resistance genes as well as group factors, such as antigens of AB0 blood group, haptoglobins etc. [8,9].

Statistical data processing in some instances is carried out incorrectly. Student's test, which is used most often while data analyzing, is only applicable to parametric indicators. In the meantime, the majority of biological subjects indicators refer to ―non-normal distribution‖, which requires use of others omnibus tests, such as, for example, Wilcoxon - Mann - Whitney test.

The nonobservance of scaled elementary planning rules of monitoring, receiving and mathematical processing of clinical laboratory data is not infrequently promotes to reception of nonrepeatable results and finding of false regularities etc.

For solution of tactical aim of objective results interpretation of clinical laboratory the following is necessary:

a. Correct mathematical analysis of laboratory patients examining results for certainty value of differences estimation from predetermined level of received laboratory indicators.

This analysis includes:

- Randomization of patient groups by sex, age, severity of disease etc. [10-13].
- Representativeness of sample – optimum patients quantity into group by Gorelik and Yakovlev's for-mula [13,14].
- Choice of appropriate statistical criterion on a normalcy of distribution basis of laboratory values. Individual valuation of immunopathic disorder is provided by the definition of parametric variation degree [9,13,15].
- Counting of diagnostic value ratio (Kj) and formation of immune system disorders formula (ISDF; three of the most

significantly changed parameters compared with standards) by it [13,15].

- Derivation of an immune correction targets formula (ICTF; three of the most strongly changed com-pared with initial level in the group) using Kj [9,13].
- Derivation of indicators displacement formula (three of the most different indicators compared with its values in patients from the control group, where patients receive one type of conventional treatments or other immunomodulator) on the basis of immune correction targets formula (ICTF) [9].
- The group estimation of immunopathology in patients population is realized in analyzing of parameters dynamics compared with predetermined level in patients group when using of:
- Frequency analysis, which use risk of pathology induction in certain indicators of 2-3 degree (degrees with + or - indicate accurate increasing or suppression of one or another key immune marker, for example, $CD56^+$ lymphocytes or $CD95^+$ monocytes etc., while table below indicates degree of these changes (2 deviation from the normal value is 34-66%; 3 deviation from the normal value is 67-100%). For example, deep deficiency of T-helper cells looks like $CD4^-3$, hyperactivation $^-CD4^+3$;
- Correlation analysis, which considers formation of strong bindings between immune and clinical indicators [1,3,16].

b. Providing of controlled clinical laboratory monitoring of patients is realized by standartization of Lebedev et al.[2,17]

- Examination term.
- Formation of appropriate control groups included healthy people, patients, which receiving conventional treatment or its combination with immunomodulators etc.
- Clinical laboratory sets of methods.
- Background therapy.
- Methods of mathematical analysis.

c. Complex analysis of immune, routine laboratorial, clinical parameters dynamics using integral indicators, such as points, ranks etc. [9,18].

d. Selection of own immunomodulators action from summary immunotropic action of all medicines, which administered for patients. This is defined by the formula of the average parameters values dynamics and frequency analysis [9].

e. Characteristics of associative processes in the laboratory field, which estimates by dynamics of strong (index of correlation more than 0.6) intrasystem (cross immune), intersystem (immune and hematological), extrasystemic (immune, biochemical and others) relations [1,3,16,19].

Reproduction of Native Immune Homeostasis Regulation

The mechanisms knowledge of such regulation is necessary. Thus, the connection between immune and nervous system is caused by ability of their elements to produce humoral regulators of both kinds of reactions. Among these regulators are interferons, interleukins, thymic peptides, Tumor Necrosis Factor (TNF), immune reactivity dependence on conditioned reflex function of CNS, association of smart memory with mechanisms of immunity, existence of universal receptors in nerve, stem, glia and lymphoid cells. Furthermore, chemical compounds, which induce processes of education (for example, growth factor) are activate immune reactions. The activators and inhibitors of neurologic memory influence on immune memory as well. It is the first mechanism.

The second mechanism is in associated function of immune and endocrine systems is explained by the fact that immunocompetent sphere is able to produce different regulatory peptide hormones, such as ACTH, TSH, STH and arginine. By comparison, the endocrine-like action is typical for immune mediators; glucocorticoid, insulin, STH and neuromodulator receptors are presence at the surface of monocytes/macrophages and lymphocytes; receptors, which may bind with antigens are founded on the surface of non-lymphoid components, such as myocardial cell; the hormones, such as ACTH, STH, estrogens, androgens and other have an effect on immune reactions dose-dependently and alternatively [20].

The third mechanism, which regulates immune homeostasis, is metabolic immunity. It consists in several factors, such as cyclic nucleotide system of cAMP – cGMP, low- and high-molecular weight nucleic acids – RNA, DNA and their fragments [18], lipid peroxidation products, diene conjugates of fatty acids, malondialdehyde, Low-Density Lipoproteins (LDL) and Very Low-Density Lipoproteins (VLDL), glycosaminoglycans, antioxidants, enzymes [4,21,22], cytochromes P-450, liver enzymes [23], allergy mediators, metabolic system (pentose phosphate cycle, glycoly-sis, tricarbonic acid cycle), erythrocytes [24] and water-salt, protein, fat and carbohydrate metabolisms [25].

The fourth mechanism is concluded in wide range of immune homeostasis endogenic regulators, which include thymic and mielopeptides, immunoglobulins and their breakdown products, albumin inhibiting factor of liver, which reduce a risk of autoaggressive reactions developing by temporary function reduction of heavy antibody [26], complement system and cytokines. This also includes phenomenon of immunogenesis continuity in consequence of irritation of lymphoid system by cross antigens of gut microflora and causative microorganisms [27].

The clinical features of disease course are the fifth factor of immunogenesis regulation. Clinical forms, pathogenesis, localization, stage, combination, diseases sensibilization were appeared to determine a significant impact on immune response developing [6].

The sixth factor is medical treatment. Using of non-drug kinds of treatment, such as bloodletting [26], low intensity laser therapy [17], plasmapheresis, ultraviolet blood irradiation, electromagnetic field effect, vaccines, sera, immunosuppressors and even size of surgical treatment influence on immunotropic action of combination therapy [6]. On the assumption of above provided information, the targeted correction of immune disorders must consider as far as possible or use of above represent natural mechanisms and reproduce them if it is necessary.

Furthermore, the new mechanisms of pharmacological correctors effects modification, which independent of their basic action and features of clinical disease progression, are indicated at the present time. It is really recognized that pathogenesis, stage, localization, sensibilization, diseases combinations, medical treatment and others are able to determine changes of immunological response components.

However, the possibility of variations of expressiveness and action mechanisms of immunomodulators is a new phenomenon.

Influence of Diseases Clinical Features on Immunocorrectors Effects

The action mechanisms of different origin immunomodulators, such as sodium nucleinate, sodium deoxyribonucleate, imunofan, glutoxim, thymogen were studied on following models: obliterative atherosclerosis, thromboangitis, cutaneous and systematic allergic vasculitis, chronic Hashimoto's thyroiditis, Chronic Obstructive Pulmonary Disease (COPD), their combinations [28], bronchial asthma in the exacerbation and remission phases, acute and chronic salpingooophoritis [29], ophtalmological and urogenital chlamydial infection, Reiter's syndrome, complication of bronchial asthma, Deep Pyoderma (DP) [30] and others diseases.

All observations were planned in the same manner. The randomization of patients groups, control of sample representativeness, formation of control group (healthy people and patients, which receiving conventional treatment or its combination with immunomodulators), and standardization of background therapy, time limits of diagnostic material sampling, biochemical and immune examination technics are preliminarily examined. Student's test or Wilcoxon — Mann — Whitney test depending on normalcy of indicators distribution are applied for statistical processing. The key indicators of initial immune system disturbances and immune correction targets are determined by diagnostic value index. Selection of own immunomodulators action from summary immunotropic action of all medicines, which administered for patients, is also estimated [1,9].

As follows from Table 1, even in patients suffering from similar pathogenesis diseases, such as obliterative atherosclerosis, thromboangiitis, cutaneous and systematic allergic vasculitis and others, the significant changes in standard variations of immune reactivity are observed. For example, in obliterative atherosclerosis the key pathological parameters are lymphocytes CD8 and CD16, pro-

Disease	Immunomodulator	ISDF	ICTF
OA	-	$CD8^{-}_{3}CD16^{+}_{3}IL8^{+}_{3}$	-
	Sodium nucleinate	-	$CD8^{+}_{3}actNBT^{-}_{2}CIC^{-}_{2}$
	Thymogen	-	$CD4^{+}_{2}CD8^{+}_{2}Lymphocytes^{+}_{2}$
TA	-	$CD8^{-}_{3}IgG^{+}_{3}CD19^{+}_{3}$	
	Sodium nucleinate	-	$CD4^{+}_{3}IgM^{+}_{3}IL6^{-}_{2}$
	Thymogen	-	$CD16^{+}_{3}IgG^{-}_{3}CIC^{-}_{3}$
CV	-	$M^{+}_{3}CD8^{-}_{3}actNBT^{-}_{3}$	
	Thymogen	-	$M^{-}_{2}IgA^{+}_{2}PC^{-}_{2}$
SV	-	$IgA^{+}_{3}CIC^{+}_{3}IL6^{+}_{3}$	
	Thymogen	-	$actNBT^{-}_{2}CD19^{-}_{2}E^{-}_{2}$
BA exacerbation	-	$L^{+}_{2}CD4^{-}_{2}CD3^{-}_{2}$	-
	Sodium nucleinate	-	$CD3^{+}_{3}PI^{+}_{3}PC^{+}_{3}$
	-	$SC^{+}_{3}CD19^{-}_{2}AMM^{+}_{2}$	-
BA remission	Sodium nucleinate	-	$CD3^{+}_{3}E^{-}_{2}SC^{-}$
	-	$L^{+}_{3}CIC^{+}_{3}CD4^{-}_{2}$	-
ASO	Glutoxim	-	$actN^{+}BT^{+}_{3}CD^{+}_{3}\ 3IL4^{+}_{2}$
AECSO	-	$E^{+}_{3}IgM^{+}_{3}IL6^{+}_{3}$	-
	Glutoxim	-	$Lymphocytes^{+}_{3}actNBT^{+}2IL8^{-}_{2}$
OCI	-	$CD3^{-}_{2}CD4^{-}_{2}CD19^{-}_{2}$	-
	Derinat	-	$CD16^{+}_{3}Lymphocytes^{+}_{3}IgG^{+}_{2}$
UCI	-	$IgM^{+}_{3}actNBT^{-}_{2}CD3^{-}_{2}$	-
	Derinat	-	$IL4^{+}_{3}CD^{+}4\ _{2}IgA^{+}_{2}$
RS	-	$CD16^{+}_{3}CIC^{+}_{3}TNF_{3}$	-
	Derinat	-	$CD8^{+}_{3}CD19^{+}_{2}IL6^{-}_{2}$
HD	-	$TAT^{+}_{3}IgG^{+}_{2}CD8^{-}_{2}$	
	Derinat	-	$CD3^{+}_{3}TAT^{-}_{2}Lymphocytes^{+}_{3}$
COPD	-	$CD4^{-}_{3}CD8^{+}_{3}CIC^{+}_{3}$	
	Derinat	-	$Lymphocytes^{+}_{3}TNF^{-}_{3}CD8^{-}_{2}$
HD+COPD	-	$Tabs^{+}_{3}CD16^{+}_{3}CIC^{+}_{3}$	
	Derinat	-	$T^{+}_{3}TSH^{-}_{2}CD16^{+}_{2}$
BA	-	$L^{+}_{2}CD4^{-}_{2}CD3^{-}_{2}$	
	Sodium nucleinate	-	$CD3^{+}_{3}PI^{+}_{3}PC_{3}^{+}$
BA+PARs	-	$SC^{+}_{3}CD3^{-}_{2}spNBTRT^{+}_{2}$	-
	Sodium nucleinate	-	$CD3^{+}_{3}CD4^{+}_{3}IL4^{+}_{3}$
DP	-	$IL8^{+}_{3}E^{+}_{3}CD8^{-}_{3}$	
	Imunofan	-	$CD4^{+}_{3}PC^{+}_{3}IL8^{-}_{3}$
DP+CA	-	$IL8^{+}_{3}CIC^{+}_{3}actNBT^{-}_{3}$	
	Imunofan	-	$PC^{+}_{3}CD8^{+}_{2}actNBT^{+}_{2}$

Table 1: Influence of pathogenisis, stage, localization, sensibilization and combination of disease on immune reac-tivity and it's differentiated pharmacological.

inflammatory interleukin-8 (IL-8), in tromboangiitis – CD8 and CD19 lymphocytes, IgG, in cutaneous vasculitis – monocytes, regulatory T-cells, activated Nitro Blue Tetrazolium Test (NBT), in systematic vasculitis – IgA, IL-6, Circulating Immune Complex (CIC).

The more great difference is observed in determining of targets for used immunomodulators in patient's immune system. For example, administering of sodium nucleinate to patients with obliterative atherosclerosis led to increasing of CD8 positive cells level, decreasing of activated nitro blue tetrazolium test and concentration of circulating immune complex. This medicine in case of tromboangiitis mainly acts on CD4 cells, IgM and IL-6. Thymogen (thymomimetic drug) in these clinical models had an effect on common regulatory and total subsets of lymphocytes or NK-cells, IgG and circulating immune complex.

In patients with surface and deep skin vasculitis Thymogen also had a differentiated effect. In the first case medicine administered led to decrease monocyte level, increase of IgA level, and retardation of phagocyte absorption function. In the second case, the suppression of neutrophils oxygen metabolism and decrease of B-lymphocytes and eosinophils amount are observed.

In patients, which suffering from bronchial asthma at the acute or remission stage, the independent from conventional treatment effect of Sodium Nucleinate was different by two of three components. This effect reflects either stimulation of positive and total CD4 lymphocytes level or stimulation of T-cells level against quantity reduction of eosinophils and immature granulocytes.

In the other clinical model of primary acute salpingo-oophoritis, Glutoxim administer has caused activation of reserve neutrophil's oxygen metabolism, accumulation of CD3 lymphocytes and anti-inflammatory IL-4. In case of secondary acute stage of disease the same immunomodulator had a stimulatory effect on lymphopoiesis, and also increased value of activated NBT and decreased IL-8 concentration.

The composition of immune correction targets formula for Derinat at various stages of chlamydiosis was different more significantly. In case of ophtalmological chlamydial infection, the targets for high-molecular DNA were NK-cells, total lympocytes, IgG; in urogenital chlamydial infection – IL-4, CD4 lymphocytes, IgA; in Reiter's syndrome - CD8 and CD19 positive cells, IL-6. In all cases, indicators dynamics from initial level was positive; ratio of change was significant of second-third degree.

The feature of diseases courses, such as high risk of allergization is exists in modern times. It is commonly supposed that about 50-60% of people in one form or another are suffering from this disease. It is necessary to distinguish true allergic reactions, which include immune mechanisms, from pseudoallergy, which developing when histamines or their liberators are entered into the organism, liver detoxicating function is disturb, formed dysbacteriosis leading to accumulation of producing histamine-like agents flora, inflammation of gastro-intestinal mucous coat with intestinal malabsorbtion is progressing, disturbances of enzymatic degradation of biogenic amines are appeared and etc.

It should be admitted that disease aggravation by allergy in addition to pathogenic changes of immune reactions is secondarily leads to this. This is occurs due to appropriate medicine administering to patients. Among these medicines there are antihistaminic, anti-inflammatory and others medicines, which also have an influence on these mechanisms.

According to above-mentioned examining algorithm, for these regularities detection the influence of pseudoallergy and cutaneous allergosis on immune reactivity changes and its correction by Sodium Nucleinate or Imunofan in patients suffering from bronchial asthma or Deep Pyoderma (DP) were studied.

It has been discovered that Pseudoallergic Reactions (PARs) formation in acute period bronchial asthma patients changes composition of Immune System Disturbance Formula (ISDF) from $L^{+}2CD4^{-}2CD3$-2 to $SC^{+}3CD3^{-}2spNBTRT^{+}2$. (L-leukocytes, SC-stab cells, spNBTRT-spontaneous Nitro Blue Tetrazolium Reduction Test).

The immune system targets for yeast low molecular RNA in both cases were T-cells, and in case of Bronchial Asthma (BA) – absorptive phagocyte activity and in case of BA^{+}PARs – CD4 positive cells and IL-4.

In case of cutaneous allergosis coupled with DP a partial change of ISDF parameters from IL8+3E+3CD8-2 to $CD8^{+}$3actNBT -3 is take place (E-eosinophil, actNBT – activated Nitro Blue Tetrazolium Test). In other words, if at the single DP the proinflammatory cytokine accumulation coupled with eosinophilia and repression of suppressive immune system component, then in case of patient's allergization the IL-8 concentration increasing combined with CIC excess and oxygen producing activity of neutrophils in peripheral blood.

The targets to Imunofan are modified accordingly. This appeared in increase of CD4 cells level, phagocytosis activation, suppressing of proinflammatory interleukin development, which promotes to phagocyte absorbtion function, accumulating of regulatory T-cells and stimulation of reserve oxygen metabolism of neutrophils.

In patients suffering from Hashimoto's Thyreoiditis (HT), COPD or their combinations, the own effect of Derinat was sufficiently expressed.

So, for example, in Hashimoto's disease the ICTF includes $CD3^{+}$3Tabs-2Lymphocytes^{+}2, in COPD – Lymphocytes^{+}3TNF-3CD8-2, in HT^{+}COPD – $T^{+}3TSH^{-}2CD16^{+}2$. (TNF-tumor necrosis factor, T-thyreoidin, TSH - thyrotropine, Tabs – autoantibodies against thyrotropine) (Table 1).

The influence of other clinical features of diseases on implementing of pharmacological correctors mechanisms is also established [9,31]. For example, in patients with viral otitis media the targets of Sodium Nucleinate are $CD8^{+}3CD4^{+}3CD19^{+}2$, in purulent (bacterial) process - $IgG^{+}3CD3^{+}3CD16^{+}3$; the interferon alfa in aseptic meningitis acted on $CD8^{+}2spNBTRT^{+}2Complement^{+}2$, in purulent meningitis - $CD19^{+}2IgA^{-}2CD8^{+}2$; the same medicine in calcu-lous cholecystitis acts on $IgM^{+}3CIC^{-}3CD19^{-}2$, in destructive cholecystitis - $CD4^{+}3IgM^{+}3L^{+}3$.

The severity of diphtheria was also a determinant factor, which affects on immunocorrection. Upon affection of nasopharynx the ICTF included Lymphocytes$^{+}2CD3^{+}2IgG^{+}3$, in combination form – $CIC^{+}3IgA^{+}3IgM^{+}3$ and in severe form - $CD3^{+}3CIC^{+}2IgM^{+}2$.

In the clinical model of erysipelatous skin inflammation the same regularity was detected. In primary lesion the Sodiun Nucleinate mainly acts on $CD16^{+}2CD4^{+}2CD8^{+}2$, in disease with rare relapses - $CD4^{+}2CD8^{+}2CD16^{+}2$ in case of frequent relapses - $CD4^{+}2CD16^{+}2CD8^{+}2$.

The degree of keratoderma injury by herpes simplex hepatitis also modified the Tactivin targets from $LMIT^{+}3CD19^{+}3IgG^{+}2$ (LMIT - leukocyte migration inhibition test) in surface form to $CD19^{+}3CD8^{+}3CD3^{+}2$ in deep form. It is significant that influence

effects are determining not only parameter set in formula, but direction and importance of changes and indicators locations.

The sufficiently demonstrative data of Sodium nucleinate targets were shown in patients with nephritic syndrome

- $PI^{+}2L^{+}2(CD8^{-}2IgA^{-}2)$ (PI - phagocytic index), nephrotic syndrome - $CD8^{+}2IgG^{+}2CD4^{-}2$, initial and relapse rhinosinusitis - $CD16^{+}2CD19^{-}2CD4^{-}2$ and $CD16^{-}2CD8^{-}2CD3^{-}2$.

The own regularities in changes of Tactivin immunoaffinity also took place in hemorrhagic and ischaemic apo-plexy Lymphocytes-$2CD8^{-}2CD3^{-}2$ and $IgG^{+}2IgA^{+}2Lymphocytes^{+}2$.

Influence of Immunoaffinity Medicine Combinations on Individual Effects of Combination Component

Polypragmasy, i.e. simultaneous administering to patients from 5 and more medicines, is currently considers as a feature of patients pharmacological treatment. The issue about possible change of actions mechanisms, for example, of immunoaffinity medicines is practically not studied. For this regularities definition the above mentioned formula of own immunomodulator action is used.

In Russian Federation more than 100 million people are treated by vaccines and serum medicines and, consequently, potential delivery of immunotherapy is obvious. The researches of this medicines influence on efficacy and targets of different immunomodulators were conducted.

Some clinical models, such as bronchial asthma, viral hepatitis B, carrier state of Australia antigen, acute oophoritis, urogenital chlamydial infection, soft tissues purulent infection and other disease were selected [1,16,23-31].

As it appears from Table 2, the administering of low-potency Rusam vaccine to patients with bronchial asthma leads to modifying of thymogen, hemodez, levamizoli, ridostin targets by two from three key figures, but sodium nucleinate targets are modifying by three key figures.

Action spectrum of low molecular RNA and high molecular DNA medicines is fully has changed on the background of the antiviral vaccine in carriers of HBS antigen and in patients with viral hepatitis B.

ICTF for combination of gammaglobulin with Ridostin was different from corresponding formulas obtained with administration of the separate components of complex modulation to female patients with acute oophoritis. The same effect was obtained with administration of Polyoxidonium and Derinat to patients with soft tissues purulent infection and urogenital chlamydial infection. Analogic regularity established during use of combination therapy different variants.

Two- or three-components of systemic modulation are used in patients suffering from urolithiasis and pyelonephritis, bronchial asthma and COPD [21]. Combination of systemic with local immunostimulants – Derinat with Superlimph and Ridostin with Superlimph in case of acute exacerbation of a chronic salpingooophoritis [28] and exacerbation of chronic suppurative otitis media in children [29] essentially change targets for separate immunomodulators.

The combinations of Imunofan and Derinat with antioxidants, such as Hypoxenum, on chronic rheumatic lung disease clinical model [20] and herpetic keratitis [21] have the same effect.

It has been established that not only complex with drug-free factor (ozonous physiological salt solution), but pathologic process localization exert modifying influence on immunocorrectors in patients suffering from ophtalmo-logical, urogenital, systemic (Reiter's syndrome) chlamydial infection.

The activity variations of pharmacology corrector's combinations of thymoptin, sodium nucleinate, myelopidum, neovir with two drug-free factors –plasmapheresis+ultraviolet blood irradiation are detected in case of corticodependent asthma [22].

More difficult regularity has documented in women with stage III breast cancer. In patients with different AB0 antigens, with the other conditions being equal, the modulating action on quantitative and qualitative characteristics of standard chemotherapy biological effects in combination with Leukinferon were noted [23].

Thus the wide spectrum of vaccines, immunoglobulins, systemic and local correctors, antioxidants, corticosteroids, cytostatics, as well as drug-free medical interventions in combination with each other is induce phenomena of targets changes and modulators effectiveness i.e. new characteristic of combination activity.

It is clear that major task of clinical immunology is not only pathogenesis study and laboratory disturbances diagnostics, but primarily creation of ideology of targeted correction as group of methods, which increase effectiveness of conventional therapy and eventually quality of patients' life.

Options of Diseases Immunotherapy

Since the activity of modulating medicines and impacts is largely

Diseases	Treatment	Mobility	ICTF
BA	CT+TG	20	$CD8^{+}{}_{3}IgM^{+}{}_{2}CD3^{+}{}_{2}$
	CT+RZ+TG	9	$CD3^{+}{}_{3}CD4^{-}{}_{3}CD8^{+}{}_{2}$
	CT+H	14	$CD19^{+}{}_{2}IgA^{+}{}_{2}ClC^{-}{}_{2}$
	CT+RZ+H	17	$CD19^{+}{}_{3}CD8^{+}{}_{2}PI^{+}{}_{2}$
	CT+Le	21	$IgM^{+}{}_{3}CD3^{+}{}_{2}IgA^{+}{}_{2}$
	CT+RZ+Le	13	$IgA^{+}{}_{3}CD8^{+}{}_{3}CD3^{+}{}_{2}$
	CT+SN	12	$CD19^{+}{}_{3}ClC^{-}{}_{3}CD8^{+}{}_{3}$
	CT+RZ+SN	11	$CD3^{+}{}_{3}CD8^{+}{}_{3}M^{-}{}_{3}$
	CT+RI	16	$CD19^{+}{}_{3}PI^{+}{}_{3}actNBT^{+}{}_{3}$
	CT+RZ+RI	8	$CD3^{+}{}_{3}CD4^{+}{}_{3}CD19^{+}{}_{3}$
Carrier state of HBV	V	3	$Lymphocytes^{+}{}_{2}IgA^{+}{}_{2}CD4^{-}{}_{2}$
	SN	4	$CD19^{-}{}_{2}PI^{+}{}_{2}CD3^{+}{}_{2}$
	D	5	$CD8^{-}{}_{3}CD11b^{+}{}_{2}IgG^{-}{}_{2}$
	V+SN	5	$CD11b^{+}{}_{2}Lymphocytes^{+}{}_{2}E^{-}{}_{3}$
	V+D	4	$Lymphocytes^{+}{}_{2}SC^{+}{}_{2}spNBTRT^{-}{}_{2}$
Chronic viral hepatitis C	CT+V	4	$CD4^{+}{}_{2}CD19^{-}{}_{2}CD8^{-}{}_{3}$
	CT+SN	4	$CD8^{+}{}_{3}E^{-}{}_{2}ALT^{-}{}_{2}$
	CT+V	5	$L^{+}{}_{2}IgA^{-}{}_{2}spNBRT^{-}{}_{2}$
	CT+V+SN	8	$CD11b^{+}{}_{2}E^{-}{}_{2}TT^{-}{}_{2}$
	CT+V+D	10	$CD16^{-}{}_{3}ALT^{-}{}_{3}E^{-}{}_{3}$
ASO	CT+RI	13	$spNBTRT^{+}{}_{3}PI^{+}{}_{3}CD4^{+}{}_{3}$
	CT+GG	8	$spNBTRT^{+}{}_{3}PI^{+}{}_{3}ClC^{-}{}_{2}$
	CT+GG+RI	12	$spNBRT^{+}{}_{3}PI^{+}{}_{3}IgA^{-}{}_{2}$
STPI	CT+P	6	$spNBRT^{+}{}_{2}IgA^{+}{}_{2}CD19^{+}{}_{3}$
	CT+GG	7	$PI^{+}{}_{2}spNDTRT^{+}{}_{2}SC^{-}{}_{2}$
	CT+GG+P	9	$IgG^{+}{}_{3}PI^{+}{}_{3}spNBTRT^{+}{}_{3}$
UCI	CT+D	10	$IL\text{-}4^{+}{}_{3}CD4^{+}{}_{2}IgA^{+}{}_{3}$
	CT+GG	6	$PI^{+}{}_{2}CD4^{+}{}_{2}SC^{-}{}_{2}$
	CT+GG+D	11	$actNBT^{+}{}_{3}spNBTRT^{+}{}_{3}PI^{+}{}_{3}$

Table 2: Influence of active and passive immunotherapy on effects and targets of immunocorrectors.

determined by their "resonance" with the natural reduction reactions of the defense reactions balance in the body, the main principle of the correction is the ability of their reproduction. In addition to this, the immunotherapy considering a complex pathogenesis of disease developing must be equally complex and multicomponent. The following options (sets) of differentiated immunocorrection are developed.

- System immunocorrection – nonspecific action on basic components of immune system (T-lymphocytes, B-lymphocytes, phagocytes) including mono-, combined, alternative immunecorrection - simultaneous in-troduction of one or several modulators, promoters and suppressors [22].
- Administration to patients of natural and synthetic analogs if immune reactions regulators – thymic and mielopeptides, interleukins, plasma transfusion, lymphocytic cells transfusion etc. [8,9].
- Using of nucleic acids native and synthetic medicines, such as sodium necleinate, ridostin, derinat, poludanum, polyinosinic:polycytidylic acid, Isoprinosine, which have the multipotent, immunomodulating, detoxicating, reparative, radioprotective and other properties [9].
- Nonspecific suppression or immune reactivity stimulation by corticosteroids, cytostatic, antihistaminic, antibacterial, metabolic and other medicines, operative trauma etc. [8,9,13].
- Induction of interferon formation by using interferon inducing agents; using of α-, β-, γ-interferons for immune reactions regulation and elimination of intracellular parasites (viruses, chlamydiae, mycoplasma and etc.) [3,16].
- Administration of antigens (vaccines) combinations or serum medicines with adjuvants/stimulators – active and passive adjuvant immunotherapy [16].
- Local immunotherapy – activation of local resistance in organs, which communicate with environment (urogenital, respiratory, digestive tract). For that purpose, superlimph, viferon, kipferon, imudon, IRS 19, vilosenum and other are used [1].
- Combined regional and systemic modulation with a stimulants combination of local and general immunity [3].
- Immune and metabolic immunotherapy - the combination of immune protection modulators with antioxidants [3,20,21].
- Complex immunotherapy - simultaneous vaccine, adjuvants, modulators and antioxidants administration to immunocompromised.
- The implementation of non-pharmacological modulation due to the use of ozonized solutions, low-intensity laser, acupuncture, perturbed magnetic field, ultraviolet radiation, plasmapheresis, sorption and other methods [26,25].
- Using a combination of pharmacological and non-pharmacological immunoaffinity effects [31-46].
- It is necessary to combine of several above mentioned units (sets) for achieve maximum therapeutic effect, taking into account pathogenic factors of defense reactions regulation in specific diseases.

Conclusion

In this article a tactic and a strategy in today's clinical immunology is taken under consideration to create an ideology of proper evaluation and correction of immune disorders. To achieve those goals it is suggested to complete a qualified plan and an objective assessment of results of clinical and laboratorial monitoring of patients, proper mathematical assessment of obtained data, and recreation of evolutionary created mechanisms, which restore the destroyed immune homeostasis. Key here is the knowledge of how the influence of clinical special features of diseases (pathogenesis, stage, localization, allergic complications etc.) on activity of modulators. It is important to use full, modularized therapy for controlled corrections in curing the immune disorders with pathological processes with complex pathogenesis. Also, a whole range of associated key problems in clinical immunology is discussed, including problems not decided to this day.

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