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Report

Results of the II phase clinical trial of Polyoxidonium use during the combined treatment of patients with atopic diseases

Responsible executor:

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Report

Clinical trial of Polyoxidonium injections (6mg, 12 mg) during the combined treatment of patients with atopic disorders

Type of the study: Open controlled
Phase of the study: IV
Number of patients: 50
Serial number of the medicine: 020195, 030195

Sponsor: "Scientific-Medical Center Petrovaks"
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Research institution:
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The leading researcher:
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Regulating standards:
The research is carried out in accordance with the requirements of Pharmacological Committee, Ministry of health, Russian Federation
The BS project "Regulations of conduction of high-quality clinical trials in Russian Federation"

General characteristics of studied medication

Polyoxidonium – the new synthetic immunomodulator pertains to the high-molecular compounds and represents the water-soluble derivate of heterochain aliphatic polyamines. Polymer chain of Polyoxidonium contains ionogenic and N-oxide groups. Polyoxidonium is the subject to bio destruction and is completely eliminated from the body. Polyoxidonium activates the phagocyte capacity of circulating neutophils, mobile macrophages and settled macrophages of the reticular-endothelial system. In addition, Polyoxidonium contributes to the co-operative interaction of T- and B-lymphocytes, migration of haemopoietic progenitors from the central to the peripheral immune organs. Significant reinforcement of antibacterial host resistance processes and antibody production as well as haemoimmunopoiesis represent the integral result of Polyoxidonium application.

Preclinical research data have established that unlike the majority of well-known immunomodulatory agents, Polyoxidonium enhances antibody production mainly owing to the production of IgG class antibodies. At the same time the production of IgE class antibodies has shown to be either not enhanced at all or to be even down regulated. This particular property of Polyoxidonium, presumably, clear the way to additional perspectives of the medication use in patients, suffering from the allergic diseases and from bronchial asthma. Present clinical trial is the first attempt to use Polyoxidonium for the treatment of patients with severe forms of atopic disorders that together with the primary disease therapy require the stimulation of antibacterial defense mechanisms of immune system.

Specific aims of the present study:

The open controlled trial was aimed at studying the tolerance and the efficiency of Polyoxidonium use during combined treatment of patients suffering from bronchial asthma, complicated with purulent bronchitis as well patients with severe atopic syndrome manifested by outspread atopic dermatitis and concomitant recurrent pyodermia.

Main tasks of the present study:

- Investigation of Polyoxidonium tolerance by the patients with severe forms of atopic disorders;

- Investigation of clinical effectiveness of Polyoxidonium inclusion in a combined therapy of patients with severe forms of atopic diseases, complicated with immune deficiency;

- Evaluation of immunomodulatory consequences of Polyoxidonium use in patients with severe forms of atopic diseases, complicated with immune deficiency;

- Comparative study of the dose-dependent and the regimen-dependent efficiency and tolerance of Polyoxidonium injections;

- Determination of indications and contraindications to the Polyoxidonium application for the treatment of patients with severe forms of atopic diseases, complicated with immune deficiency.

Research type

There have been carried out the open clinical trials, which implied the participating physicians and patients preliminarily informed on the application of immunostimulatory agent - Polyoxidonium.

Taking into account the increased risk of allergy or asthma exacerbation resultant from the use of any immunostimulatory agent by patients with respective diseases, it seemed impossible to encode the flasks with polyoxidonium or placebo during as in the previous studies. Asthma/allergy aggravation would require the administration of urgent anti-allergy and anti-shock measures. Therefore, it was determined to carry out the open trials aimed primarily at evaluation of tolerance and the principal possibility of Polyoxidonium use in patients with atopic disease. In addition to medication tolerance, the curative effect of Polyoxidonium on purulent-septic processes accompanying and complicating the primary atopic disease has been studied.

Patient enrollment criteria

The following two inclusion criteria were considered on patient's enrollment in the research:

1. The diagnosis of serious atopic disease – severe allergy or bronchial asthma
2. Concomitant atopic suppurative-septic complications conditioned by the insufficiency of host resistance potency that intrinsically, represent the pathogenetic indication for the use of immunostimulatory agent.

Clinical, immunological and allergological characteristics of patients

50 patients that comprised the following two study groups had been included in a research:

I group was composed of 27 patients suffering with the atopic bronchial asthma with moderate or severe clinical course. The primary disease was complicated with chronic obstructive or suppurative-obstructive bronchitis. The patients' age ranged from 23 to 42 years. 17 women and 10 men were included in this group. The duration of case history was from 3 months up to 26 years.

The manifestations of immune deficiency - mainly, the recurrent chronic obstructive and suppurative-obstructive bronchitis, accompanied by the candidiasis of mouth and pharynx in 7 patients, by the grade-2 intestinal disbacteriosis in 4 patients and by the chronic recurrent herpes virus infection in 7 participants were observed in all patients of I group.

The following concomitant diseases were explored in this study group: polypous maxillary sinusitis and ethmoiditis – in 6 patients, chronic gastroduodenitis – 19 patients, chronic cholecystitis – 5 patients and grade-2 struma without function impairment – 2 patients.

General examination of patients revealed the following alterations:
Complete blood count:
- Increase in band neutrophils (7 to 12%) in 4 patients;
- Increase in eosinophils (7 to 15%) in 5 patients;
- Increase in white blood cell count ($7x10^9$/l to $8,4x10^9$/l) in 4 patients.

Clinical and biochemical values of blood and urine tests, as well as electrocardiography failed to show any pathologic changes.

Pulmonary function testing revealed the grade–1 lung ventilation obstructive alteration in 21 patients and grade–2 obstructive disturbance of lung ventilation in 6 patients. Prolongation of airflow rates in large as well as smaller airways was observed in all patients.

The flexible fiberoptic bronchoscopy showed grade–1 bilateral diffuse endobronchitis in 6 patients, grade–2 bilateral diffuse endobronchitis in 8 patients, grade-1 tracheobronchial dyskinesia in 4 patients and grade-2 tracheobronchial dyskinesia in 8 patients.

Bacteriological culture tests of sputum and bronchial contents derived from the study group participants explored Str. viridans in 6 patients, Str. hemolyticus – 3 patients, Neisseria subflava – 5 patients, Staph. aureus - 2 patients and Candida albicans - 2 patients.

Additional 23 patients that had been suffering from the severe atopic syndrome manifested in outspread atopic dermatitis complicated with pyodermia and dermal candidiasis were included in **II group**. Besides these disorders, all patients showed clinical signs of respiratory tract atopic disorders in the form of bronchial asthma, allergic rhino-conjunctivitis or polynosis. 11 men and 12 women were enrolled in this study group. Participants' age ranged from 20 to 31 years. The case history lasted from 4 months up to 26 years.

Gastrointestinal tract disorder in the form of chronic gastroduodenitis was explored on investigation of concomitant diseases in all participants of II group. 4 patients showed chronic cholecystitis in addition to chronic gastroduodenitis. All patients proved to have chronic bacterial or fungal disorders: 3 patients suffered from chronic pyelonephritis, 6 patients – from chronic tonsillitis above exacerbation, 16 patients – intestinal dysbacteriosis. All patients exhibited manifestations of asthenic-neurotic syndrome.

Clinical signs of immunodeficiency – All patients from this study group had chronic recurrent pyodermia that was combined with candidiasis of mouth and pharynx in 5 patients, with intestinal dysbacteriosis in 16 patients, with chronic bronchitis in 1 patient and with chronic herpes virus infection in 3 patients.

The laboratory findings on patients clinical examination revealed the following alterations:
Complete blood count:

- Increase in eosinophils (8 to 15%) in all patients;
- Increase in white blood cell count ($7x10^9$/l to $15x10^9$/l) in 6 patients;
- Increase in band neutrophils (to 11%) in 3 patients;

Clinical and biochemical values of blood and urine tests, as well as electrocardiography failed to show any pathologic changes.
Bacteriological culture tests of specimens from pharynx and nose mucosa as well as skin surface explored Str. viridans in 7 patients, Staph. aureus - in 5 patients, Str. pyogenus - in 4 patients, E. coli - in 2 patients. All patients showed sensibilization to certain atopic allergens on allergy testing.

Doses and regimens of Polyoxidonium injections

The following treatment regimens have been used:

1. Polyoxidonium – 6 mg intramuscular injections on alternate days. The total course consisted of 5 injections;
2. Polyoxidonium – 12 mg intramuscular injections on alternate days, in total - 5 injections.

Criteria for the evaluation of clinical trial results

Criteria for Polyoxidonium tolerance evaluation

The main indicators of tolerance to the medication were as follow:

- Development of either immediate or delayed reactions manifested by the local irritation, inflammation or allergy in the site of injection or approximate to it.
- Development of either immediate or delayed systemic allergic reactions on medication injections;
- Occurrence of either immediate or delayed subjective sensations including complaints about enforcement of fatigue, advent of chills, dizziness, palpitations, suffocation, feeling of hot or pain of any localization that were ascribed to Polyoxidonium injections by the patients;
- Advent of either immediate or delayed objective signs of systemic reactions precipitated by the agent injection and manifested by considerable changes in body temperature, heart rate and blood pressure as well as basic laboratory findings of blood and urine tests.

Clinical efficiency criteria of medication use

Clinical effectiveness of adjuvant Polyoxidonium treatment in patients with atopic diseases was evaluated using the following criteria:

- Absence of aggravation of primary atopic disease and chronic infection;
- Reduction in requirements of basic treatment of primary atopic disease;
- Improvement of functional characteristics of external respiration in patients with bronchial asthma complicated with obstructive bronchitis;
- Favorable dynamic changes in endoscopic images of airways in patients with bronchial asthma complicated with obstructive bronchitis;
- Normalization of complete blood count values;
- Dynamic changes in immunological findings of blood tests.

The results of clinical trial of Polyoxidonium

Polyoxidonium tolerance

None of 50 patients, who had undergone Polyoxidonium injections exhibited either immediate or delayed adverse effects on medication. The maximal follow-up period lasted up to 5 months.

According to accomplished tests, single dose (6 mg and 12 mg) intramuscular injections might be considered to be the safe and well-tolerated adjuvant for the treatment of patients with severe forms of atopic diseases. The absolute safety and tolerance of medication given

at 30 mg to 60 mg total doses, 5 intramuscular injections in accordance with either schedules have been established.

The both schedules of Polyoxidonium use at 6mg and 12 mg single doses (30 mg and 60 mg course doses, respectively) proved to be the effective adjuvant to the combined therapy of patients with atopic disorders complicated with chronic purulant-septic processes. Thus, 96% (48 patients out of 50) of patients, who had received Polyoxidonium treatment, achieved complete remission of the primary atopic diseases as well as that of concomitant chronic infectious-inflammatory disorders, resultant from the immune deficiency. 2 patients out of 50 showed the exacerbation of concomitant purulant process. The status aggravation was attributed to the development of severe viral infection of respiratory tract during the ongoing research.

Results of Polyoxidonium injections in accordance with I schedule

I group – 27 patients received Polyoxidonium injections at 6 mg single dose on alternate days, in total - 5 injections. The treatment was administered in the period of clinical manifestations of primary disease and aggravation of chronic obstructive or purulant-obstructive bronchitis. In addition to Polyoxidonium, the xanthine derivates, cromolyn medications and mucolytics were included in combined treatment. Glucocorticoids were not given to patients during the Polyoxidonium use. 15 patients received antimicrobials that were chosen in accordance with bacteriologic culture and sensitivity study results.

Reduction in intensity of atopic disorders and in requirements of broncholytic agents

Polyoxidonium was well tolerated by I group patients and the medication adverse effects were not stated in this group. Polyoxidonium use did not result in aggravation of the primary atopic disease symptoms either. On the contrary, decrease in requirements of anti-allergy/anti-asthma medications, namely, the reduction in β_2-agonists' use on brocholytic purposes, has been observed during Polyoxidonium therapy and subsequent follow-up periods. The broncholytic therapy by β_2-agonists was completely discontinued in a number of cases of Polyoxidonium application.

Improvement in objective findings of pulmonary function testing

Pulmonary function evaluation revealed the pronounced improvement in values of external breathing. In particular, elevation in Vital Capacity (VC) from 3,31 to 5,05 liters, as well as in Forced Vital Capacity (FVC) from 3,44 to 4,44 liters. Values of airway flow rate of large as so as small bronchi have significantly enhanced.

Reduction in objective signs of inflammatory disease manifestations in bronchi

Beneficial changes were observed on repeated bronchoscopy. Repeated test results are listed in the Table 1. Reduction in alterations that were visualized on repeated bronchoscopy contributed to decreased number of patients with severe tracheo-bronchial dyskinesias and to the shift of these patients into the group of grade-1 diffuse endobronchitis. In other words, pathomorphologic characteristics of primary disease have been considerably reduced following combined therapy including polyoxidonium.

Table 1. Dynamic changes in endoscopic images that were visualized during the polyoxidonium treatment of patients with bronchial asthma, complicated with chronic obstructive bronchitis

Endoscopic findings	Number of patients with pointed pathomorphological alterations	intensity of in bronchi
	Before treatment	After treatment
Grade-1 bilateral diffuse Endobronchitis	8	19
Grade-2 bilateral diffuse Endobronchitis	9	3
Grade-1 tracheo-bronchial dyskinesis	5	3
Grade-2 tracheo-bronchial dyskinesis	5	1

Improvements in hematological values

Reduction in pathologically elevated band neutrophils (young forms of leukocytes) was revealed following Polyoxidonium treatment. This observation serves to be the evidence of alleviating systemic manifestations of inflammatory disease of bacterial etiology. At the same time, the unbiased reduction in the intensity of local signs of bronchitis was explored on bronchoscopy. In other words, there has been shown the direct correlation between the effective treatment of bronchitis and normalization of complete blood cell count. In addition, elevation in numbers of monocytes and lymphocytes testifying to the activation of the mentioned major immunocompetent cells took place during Polyoxidonium injections. The rest hematological values remained constant.

Table 2. Dynamic changes in values of complete blood count in patients with bronchial Asthma, complicated with chronic obstructive bronchitis during the Polyoxidonium treatment

Values	Before treatment	After treatment
Hemoglobin, g/l	141,0 ± 12,9	139,0 ± 11,3
Leukocytes, $x10^9$/l	6,44 ± 1,03	6,57 ± 1,34
Band neutrophils, %	6,34 ± 1,71	4,84 ± 0,78
Segmented neutrophils, %	54,75 ± 9,01	50,36 ± 9,84
Lymphocytes, %	26,38 ± 8,37	29,71 ± 8,97
Eosinophils, %	5,09 ±4,68	5,18 ± 4,21
Basophils, %	0,19 ± 0,04	0,11 ± 0,29
Monocytes, %	9,38 ± 4,13	9,86 ± 3,06
ESR, mm/hour	11,0 ± 6,08	12,14 ± 6,47

Biochemical values of blood tests

The biochemical blood test results of patients enrolled in the given study group are enumerated in Table 3. Significant changes were not found in biochemical values of blood tests accomplished during Polyoxidonium therapy. This condition corroborates the hepatic and renal safety of Polyoxidonium use.

Table 3. Dynamic changes in biochemical values of patients from I study group during Polyoxidonium treatment

Values	Before treatment	After treatment
Total protein, g/l	73,06 ± 5,0	68,33 ± 4,61
Blood urea nitrogen, mmol/l	4,55 ± 1,05	5,14 ± 1,18
Creatinine, mcmol/l	103,31 ± 21,62	98,38 ± 10,24
Bilirubin, mcmol/l	9,36 ± 2,74	7,99 ± 1,54
Cholesterine, mmol/l	4,99 ± 1,45	5,00 ± 1,23
ALT, u/l	8,19 ± 2,29	8,33 ± 2,96
AST, u/l	10,38 ± 2,03	9,89 ± 2,57
Tymolic test, u	3,17 ± 0,95	2,78 ± 1,26
Sulemic test, l	0,0016 ± 0,000076	0,00164 ± 0,000124

Normalization of immunological findings

The immunological tests were performed before treatment, after the Polyoxidonium treatment course accomplishment and 14 days after. The dynamic alterations of immunological test findings are depicted in Table 4.

As it has already been mentioned before, the absolute lymphoid cell count and number of lymphocytes pertaining to certain subpopulations were increased. In particular, lymphocyte count had elevated from $1,65x10^9$/l to $1,95x10^9$/l. Significant enhancement in total numbers of CD3+ cells (from 1030 to 1320) and especially, in that of CD4+ T cells (from 580 to 760) was revealed. The minor increase in cytotoxic lymphocyte count was observed: CD8+ T-cells – from 390 to 460, and NK-cells – from 95 to 110. B-lymphocyte count remained stable during Polyoxidonium treatment.

Immunoregulatory index represents one of the major characteristics of immune status. The immunoregulatory index values were significantly increased in patients undertaking Polyoxidonium treatment that undeniably was attributed to the absolute CD4+ T-cell count elevation.

Polyoxidonium effect contributes to the considerable activation of phagocytic granulocytes, which was confirmed by the intensification of zymosan (agent that contains microbial components) effect on the cellular metabolism in neutrophils. The index of neutrophil reaction on zymosan was almost doubled (increased from 20 to 39). Neutrophil activity strengthening effect of the medication had been maintained for 14 days after the completion of Polyoxidonium injections.

Increase in IgA and IgM class immunoglobulin concentrations was revealed following the Polyoxidonium therapy. It is well known, that IgA class antibodies mediate the main antimicrobial and antitoxic host defense mechanisms that take effect in

intrabronchial and intraalveolar spaces. Therefore, stimulatory effect of Polyoxidonium on IgA production provides the evidence of extremely favorable influence of given medication on pathogenetic disturbances in patients with chronic respiratory disorders. The major activity of IgM class antibodies is related to the opsonic adherence of microbes and other "foreign" particles that are prone to phagocytosis. Thus, increase in IgM production and stimulation of functional activity of phagocytic cells must lead to the synergic effect – efficacious activation of phagocytosis of opsonized bacteria.

Table 4. Dynamic changes in immunological values during Polyoxidonium treatment of patients with bronchial asthma complicated by chronic bronchitis

Values	Before therapy	After therapy	14 days later
Leukocytes, x 10^9/l	6,44± 1,03	6,57 ±1,34	6,48 ± 1,27
Lymphocytes, %	26,38 ± 8,37	29,71 ± 8,97	29,71 ± 8,76
Lymphocytes, x 10^9/l	1,69 ± 0,09	1,95 ± 0,12	1,95 ± 0,12
CD3+ cells, %	61,0 ± 9,33	66,95 ± 10,48	67,91 ± 9,16
CD3+ cells, x 10^9/l	1,03 ± 0,008	1,31 ± 0,013	1,32 ± 0,011
CD4+ cells, %	34,39 ± 8,67	37,84 ± 7,43	39,33 ± 7,87
CD4+ cells, x 10^9/l	0,58 ± 0,007	0,73 ± 0,009	0,76 ± 0,01
CD8+ cells, %	23,0 ± 8,9	21,69 ± 6,35	23,5 ± 7,89
CD8+ cells, x 10^9/l	0,39 ± 0,008	0,42 ± 0,007	0,46 ± 0,009
CD16+ cells, %	5,67 ± 4,03	5,8 ± 3,12	5,56 ± 4,67
CD16+ cells, x 10^9/l	0,095 ± 0,003	0,11 ± 0,003	0,11 ± 0,005
B-cells, %	6,4 ± 4,15	6,06 ± 4,35	5,33 ± 2,67
B-cells, x 10^9/l	0,11 ± 0,004	0,12 ± 0,002	0,10 ± 0,003
HLA-DR	10,36 ± 6,67	7,40 ± 5,27	7,75 ± 3,28
Spontaneous chemiluminescence	38,86 ± 22,03	45,38 ± 24,5	44,36 ± 21,24
Stimulated chemiluminescence	310,1 ± 151,4	331,6 ± 169,6	451,8 ± 200,3
Stimulation index	20,5 ± 14,7	35,0 ± 13,3	39,4 ± 25,0
IgA	278,5 ± 29,6	326,13 ± 29,7	366,75 ± 31,3
IgG	1152,16 ± 119,3	1203,5 ± 101,7	1190,0 ± 98,6
IgM	138,8 ± 11,6	166,13 ± 15,4	174,0 ± 13,03

Results of Polyoxidonium injections in accordance with II schedule

II group – each of 23 patients from given study group received 5 intramuscular injections of Polyoxidonium at 12mg single dose on alternate days. Total course dose equaled 60mg that was the doubled dose in comparison with that used in I schedule. Taking into account the existing high risk of exacerbation of allergic/atopic symptoms in patients receiving immunomodulatory treatment, commencement of high-dose Polyoxidonium injections (II schedule) became possible only after the irrefutable establishment of medication tolerance due to low-dose injections performed in adherence to the I schedule.

High tolerance and effectiveness of therapy according to the clinical signs

Patients enrolled in the given (II) study group undertook therapy in connection with atopic dermatitis and aggravation of pyodermia. The systemic antihistamine agents and

detoxification therapy as well as local glucocorticoids-containing ointments, antiseptic agents and physiotherapy procedures were administered in addition to the Polyoxidonium injections. 18 patients received antimicrobials chosen in accordance with bacteriologic culture and sensitivity study results.

High-dose Polyoxidonium injections were well tolerated by all patients from II group. None of 23 patients included suffered from either systemic or local as well as either immediate or delayed adverse effects.

All 23 patients showed significant reduction in manifestations of suppurative-inflammatory disorders following Polyoxidonium treatment: the drastic reduction and even complete disappearance of purulant lesions were observed; the general intoxication symptoms such as fever, weakness, sweating disappeared completely. At the same time, significant regression of atopic dermatitis was revealed following treatment. 17 out of 23 patients achieved complete remission of dermatitis.

Normalization of hematological values

Repeated clinical blood tests accomplished before and following the Polyoxidonium treatment revealed the dynamic changes in the complete blood cell count (depicted in the Table 5). Significant decrease in band neutrophil count was considered to be one of the most prominent observation. It is well established that increase in band neutrophil percentage heralds the development of purulant-inflammatory process. Thus, the patients have shown reduction in intensity of the most pronounced laboratory indicator of suppurative inflammation. Percentage and absolute count of band neutrophils decreased to 5,5% and $0,37x10^9$/l, respectively, due to Polyoxidonium therapy, in comparison with values observed before treatment 8,7% and $0,68x10^9$/, respectively. At the same time, the white blood cell count fell from $8x10^9$/l to the "near healthy" level – $6 x10^9$/l. The absolute lymphocyte count increased from $1,8 x 10^9$/l to $1,95 x 10^9$/l and on the contrary, the absolute monocyte count reduced from $0,7 x 10^9$/l to $0,5 x 10^9$/l during the follow-up period. Hence, all peripheral blood cell values showed the tendency towards normalization by virtue of Polyoxidonium use during the combined treatment of patients with atopic disorders, complicated with purulant-septic process.

Table 5. Dynamic changes in complete blood cell count of patients with severe atopic syndrome before and following the Polyoxidonium treatment
(II schedule - 12 mg x 5)

Values	Before treatment	After treatment
Hemoglobin, g/l	145,5 ± 14,3	141,71 ± 13,1
Leukocytes, $x10^9$/l	7,87 ± 1,12	6,76 ± 1,09
Band neutrophils, %	8,74 ± 1,76	5,54 ± 1,23
Band neutrophils, $x10^9$/l	0,68 ± 0,16	0,37 ± 0,013
Segmented neutrophils, %	59,25 ± 10,01	53,86 ± 9,78
Segmented neutrophils, $x10^9$/l	4,66 ± 0,11	3,64 ± 0,10
Eosinophils, %	4,92 ± 2,3	7,71 ± 3,51
Eosinophils, $x10^9$/l	0,38 ± 0,025	0,52 ± 0,038
Basophils, %	0,42 ± 0,07	0
Basophils, $x10^9$/l	0,033 ± 0,0008	0
Lymphocytes, %	22,59 ± 5,56	28,98 ± 4,56
Lymphocytes, $x10^9$/l	1,78 ± 0,06	1,95 ± 0,05
Monocytes, %	9,64 ± 4,11	7,66 ± 3,12
Monocytes, $x10^9$/l	0,76 ± 0,05	0,53 ± 0,034
ESR, mm/hour	18,71 ± 6,31	17,0 ± 4,97

Evaluation of Hepatic and renal safety of Polyoxidonium injections according to biochemical blood test values

II group patients did not show any considerable alterations in biochemical values of blood tests (Table 6) that proved to be the evidence of good tolerance and safety of Polyoxidonium injections in connection with functions of vital organs such as liver, pancreas and kidneys.

Table 6. Dynamic changes in biochemical values of patients with severe atopic syndrome during the Polyoxidonium treatment in accordance with II schedule (12 mg x 5)

Values	Before treatment	After treatment
Total protein, g/l	70,1 ± 4,15	72,61 ± 5,03
Blood urea nitrogen, mmol/l	4,8 ± 1,03	5,07 ± 1,15
Creatinine, mcmol/l	100,83 ± 21,6	100,4 ± 20,98
Bilirubin, mcmol/l	8,19 ± 1,61	8,36 ± 1,73
Cholesterine, mmol/l	4,76 ± 1,45	3,9 ± 1,08
ALT, u/l	7,0 ± 2,13	6,6 ± 1,98
AST, u/l	8,71 ± 2,76	8,6 ± 2,75
Glucose, mmol/l	4,89 ± 0,49	4,28 ± 0,43
Tymolic test, u	3,44 ± 0,95	3,4 ± 0,93
Sulemic test, l	0,00156 ± 0,00012	0,00156 ± 0,00013

The pronounced immunostimulatory activity of Polyoxidonium according to immune status values

Immunological tests were performed before treatment, the day after the completion of Polyoxidonium injections and 14 days after the immunomodulatory therapy. The dynamic changes in immunological findings during adjuvant Polyoxidonium therapy of patients with severe atopic syndrome complicated with pyodermia are summarized in Table 4. Activation of neutrophil reaction to zymosan (chemiluminescence induced by luminole) is considered to be one of the most significant alterations that corroborate the stimulatory influence of Polyoxidonium on one of the fundamental mechanisms of phagocytosis and antimicrobial host defense. Like I group, II group patients exhibited normalization of leukocyte count and considerable increase in lymphocyte percentage (from 23% to 29%) on Polyoxidonium treatment. In particular, the elevation of CD3-positive T-lymphocyte percent from 66% to 73% as well as that of absolute number from 1190 to 1430 turned out to be the noticeable finding. In spite of the fact that the total number of B-lymphocytes remained constant, IgA production showed substantial increase. In total, alterations of immunogramm values observed in II group were similar to those found in patients treated in adherence to I schedule of Polyoxidonium injections. Regardless of Polyoxidonium dose (6 mg or 12 mg), regression of the suppurative inflammation and the considerable strengthening of major host defense mechanisms such as IgA production as well as the activity of phagocyting cells and lymphocytes were explored in both groups.

Table 7. Dynamic changes in immunological values of severe atopic syndrome patients following II schedule Polyoxidonium therapy

Values	Before therapy	After therapy
Leukocytes, x 10^9/l	7,87 ± 1,12	6,76 ±1,03
Lymphocytes, %	22,59 ± 5,56	28,89 ± 4,56
Lymphocytes, x 10^9/l	1,78 ± 0,06	1,95 ± 0,05
CD3+ cells, %	66,67 ± 10,86	73,5 ± 10,01
CD3+ cells, x 10^9/l	1,19 ± 0,0065	1,43 ± 0,005
CD4+ cells, %	45,75 ± 6,55	43,17 ± 12,17
CD4+ cells, x 10^9/l	0,81 ± 0,004	0,84 ± 0,006
CD8+ cells, %	23,25 ± 7,14	24,40 ± 6,85
CD8+ cells, x 10^9/l	0,41 ± 0,004	0,48 ± 0,003
CD16+ cells, %	6,80 ± 4,09	5,8 ± 4,44
CD16+ cells, x 10^9/l	0,12 ± 0,002	0,11 ± 0,08
B-cells, %	8,2 ± 1,92	7,83 ± 6,82
B-cells, x 10^9/l	0,145 ± 0,001	0,15 ± 0,003
Spontaneous chemiluminescence	89,5 ± 22,6	13,75 ± 6,76
Stimulation index	20,5 ± 14,7	35,0 ± 13,3
IgA	268,14 ± 28,6	323,16 ± 29,3
IgG	1368,71 ± 129,6	1252,0 ± 115,8
IgM	146,66 ± 12,8	154,16 ± 14,4

Conclusion

The following conclusions might be drawn based on research data:

1. Polyoxidonium administered intramuscularly at 6 – 12 mg single dose on alternate days, 5 injections per course – is well tolerated by patients with severe atopic disorders (bronchial asthma, atopic dermatitis).
2. Polyoxidonium exert pronounced influence on fundamental mechanisms of host defense - in particular, on the phagocyte and lymphocyte activity as well as on IgA and IgM synthesis in patients with severe atopic diseases accompanied by the manifestations of functional immune deficiency.
3. Good tolerance and marked immunostimulatory effect of Polyoxidonium provide highly beneficial efficiency of medication use for the treatment of chronic purulant-septic processes in patients with severe forms of atopic disorders. The achieved clinical effects promote to recommend the medication for the wide application in allergological practice.
4. Polyoxidonium yields efficient combination with the traditional medications (antihistamine, broncholytic, corticosteroid, beta-agonist and antibiotic agents) that are widely used for the treatment of patients with allergic/atopic diseases. Therefore, inclusion of Polyoxidonium into the traditional treatment regimens is strongly recommended. It will promote elevation of treatment effectiveness in patients with atopic disorders, especially, in cases of profound immune deficiency, when the patient suffers seriously from the chronic recurrent inflammatory processes.
5. Combination of Polyoxidonium with the traditional anti-allergy treatment resulted in reduced severity, rate and duration of chronic inflammatory disease. In addition, it contributed to stable remission of primary atopic disease.
6. The obtained data proved to be the basis for the statement that the both – 6 mg and 12 mg – doses of Polyoxidonium (30 mg and 60 mg, respective course doses) are equally well-tolerated by patients with severe atopic diseases. The both doses showed pronounced immunostimulatory effect providing high efficiency of treatment of suppurative-inflammatory diseases and contributing to the stable complete remission of primary atopic disease. Significant distinctions in therapeutic effects between the different – 6 mg and 12 mg - doses of Polyoxidonium injections have not been observed.

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“Approved”	“Concerted”
“----- “ ---------- 1996 yr	“------ “ ---------- 1996 yr
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