Research Article

Immunotherapy in the treatment of chronic cystitis

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Abstract

Introduction: The article deals with to the new approaches to the immunotherapy of chronic cystitis. Cystitis appears to be a disease linked to the decreased immunity of the population.

Materials and Methods: The study included 200 patients with chronic cystitis, and was performed in three stages. At the first stage, all 200 patients were questioned to determine whether they do or do not have the basic immunopathological syndromes. At the second stage, the patients of 6 clinical groups underwent a routine immunologic examination using tests to evaluate basic populations, lymphocyte subpopulations, immune globulins, circulating immune complexes, average weight molecules, absorbing and metabolic phagocytic ability, pro- and anti-inflammatory cytokines by using flow cytofluorometry methods. The third stage included distribution of the major group of patients with chronic cystitis in the relapse stage into subgroups of 25 patients each who received conventional therapy.

Results and Discussion: The study has the following findings: the formation of risk groups depends on immunopathological syndromes and clinical-laboratory markers of disease peculiarities; signal tests of immunologic disorders and their correlative links with metabolic stress parameters were specified and formalized as diagnostic formulas; high clinical-bacteriological and low hemato-immunological efficacy of the conventional therapy patients with chronic cystitis and the capacity of the local and systemic modulators, such as kipferon, superlimf and imunofan, galavit, and their combinations, to normalize the parameters under study during 7-10 days were demonstrated. When combining the correctors, it was possible to achieve new quality independent of the properties of individual agents included in the composition; the reveal targets of various immune therapies were conditioned by the treatment provided, the characteristics of the correctors, the identification period – 7-10 days – 3-4 months. The analysis of the formulas of modulator targets made it possible to identify laboratory findings for their selection.

Conclusion: The data obtained during the study support the fact that there was no clinical efficacy of the conventional therapy for patients; this efficacy was maintained through to the administration of the combination of modulators in the acute period. Substantiated differentiated immunotherapy resulted in implementing the proper algorithm of observations, which prevented recurring of chronic cystitis in 3-4 months.

Keywords

immunomodulators, immunopathological syndrome, clinical-laboratory markers, conventional pharmacotherapy

Introduction

The incidence of cystitis has increased recently (Hauser et al. 2016). This appears to be related to the decreased collective immunity of humankind, changes in the demographic situation resulting in an increased shyare of senior citizens in the population, including women in the climacteric period, and insufficient efficacy of the con-

ventional antibacterial therapy ignoring immunologic disorders in patients (Zemskov et al. 2016).

A certain research design algorithm was developed to obtain the **study objectives**: to increase the efficacy of the traditional cystitis therapy through valid differentiated immunotherapy.

Materials and methods

The plan of clinical research was presented at the meeting of the Ethics Committee of Voronezh N.N. Burdenko State Medical University of the Ministry of Healthcare of the Russian Federation and in compliance with the provisions of the Declaration of Helsinki on medical ethics.

The study included 200 patients with chronic cystitis in the relapse stage (group 1), 24 patients with acute cystitis (group 2), 20 patients with chronic cystitis in the relapse stage combined with chronic pyelonephritis (group 3), and 22 patients with chronic cystitis in the relapse stage combined with chronic salpingo-oophoritis in the relapse stage (group 4). A group of comparison included 30 healthy people of similar age. All the patients participating in the study were diagnosed using conventional methods.

At the first stage of the study, using pre-laboratory methods, all the 266 patients were interviewed to reveal presence or absence of basic immunopathological syndromes – immunodeficient, infectious, allergic, autoimmune, and lymphoproliferative (Zemskov et al. 2013). The patients withut any syndrome were included in the no-risk group; the patients with one of these syndromes were included in the risk group; the patients with a combination of syndrome were included in the group of increased risk (Zemskov et al. 2017).

At the second stage, the patients of 6 clinical groups underwent a routine immunologic examination using 26 tests to evaluate basic populations, lymphocyte subpopulations, immune globulins, circulating immune complexes, average weight molecules, absorbing and metabolic phagocytic ability, pro- and anti-inflammatory cytokines by flow cytofluorometry methods. In the obtained body of data, cellular, humoral, phagocytic, cytokine reactions were assessed by means of the rank-ordering method depending on what component of the immune system the indicators refer to. Signal tests of disorders were selected using the coefficient of diagnostic considerations (Bollestad et al. 2018).

At the third stage, the main group of patients – group 1 – was categorized into 6 subgroups, 25 people each; they were given conventional therapy: with monural, fluoroquinolones, semisynthetic antibiotics with urogenous septics (nitrofurantoin, furaginum), symptomatic medications, etc. Kipferon (Kf), superlimf (Sl), imunofan (If), galavit (Gl) and the combination superlimf+imunofan (Sl+If) were used as local and systemic modulators.

Prior to the therapy and 7-10 days after the treatment onset, the incidence of the following parameters was determined in patients:

– clinical symptoms of the urinary syndrome – frequent urination, urge urinary incontinence, cloudy urine, foul-smelling urine, leukocyturia, terminal hematuria;
– intoxication syndrome – lower abdominal pains, subfebrile condition, intoxication;
– bacteriologic indices – bacteriuria, *E. coli* isolated from the urine, unidentified gram-negative microflora (GN), sterile urine samples;
– modified routine hematologic markers of inflammation;
– immunologic parameters.

In 20 patients receiving conventional therapy and in 20 patients receiving conventional therapy in combination with superlimf+imunofan, the above-mentioned tests were done again 3-4 months later.

In addition, the metabolic status was assessed in 20 patients of group 1 (chronic cystitis in the relapse stage): parameters of free-radical lipid and protein oxidation (FRO), antioxidant defense (AOD) - diene conjugates (DC), ketodienes (KD), malondialdehydes (MDA), bi-tyrosine cross-links (BC). Super oxide dismutase (SOD), catalase (C), vitamin E (VE), systemic thiols (ST) were detected in the AOD system.

Mathematic analysis of the obtained data

At the stage of the study design, the patients' groups and subgroups were randomized according to their gender, age, severity of the disease on the basis of random normal numbers and the representativeness of sample using the formula by L.E. Kholodova and V.P. Yakovleva. (Zemskov et al. 2008).

Several types of rank formalized assessment of the variations of 9 clinical, 4 bacteriologic, 5 hematologic and 26 immunologic findings grouped depending on certain associations were used to measure comparative efficacy of the differentiated immunotherapy of chronic cystitis in the relapse stage. The analysis was made on: a mobile effect characterized by the proportion of parameters which had significantly changed compared to the initial level, a normalizing action compared to the normative parameters in healthy people from the comparison group, diviation from the efficacy of one type of conventional treatment, a mean percentage of diviation from the norm in patients categorized by methods of examination. An integral evaluation was performed in ranks on the following scale: insignificant (rank 3) – when the parameter had significantly changed in 0-33% of the patients, mean (rank 2) – when the parameter had significantly changed in 34-66% of the patients, significant (rank 1) – when the parameter had significantly changed in more than 66% of the patients.

Signal tests of disorders were selected using the coefficient of diagnostic considerations calculated by the formula (Gorelik and Skripkin 1974):

$$Kj = \frac{2 \cdot (\delta_1^2 + \delta_2^2)}{(M_2 - M_1)^2}$$

where δ1 and δ2 were mean square deviations, M_1, M_2 were mean parameters of the compared groups. The signal tests of disorders were selected with the following interpretation: the less was Kj module, the higher was the level of diviations from the determined level.

Signal parameters were formalized in typical formulas: the formula of the immune system disorders (FISD) calculated in relation to the normative parameters in healthy people; the formula of targets of immunocorrection (FTI) which were calculated in relation to the initial parameters; the formula of "proper" targets of immunocorrection (FTI_{prop}) calculated in relation to the conventional therapy.

Optimality of the immune system reaction was indirectly characterized by the definition of intra-, inter-, extrasystemic strong correlative links with the coefficient > 0.6 of pivotal parameters of FISD (Zemskov et al. 2017)

By means of the inversive backward analysis of the composition of FTI, the laboratory markers were defined for selecting medications (Gevorkyan 2017)

Results and discussion

Clinical laboratory markers of risk groups of immunopathological syndromes in patients suffering from chronic cystitis

The results of the interview demonstrated that, out of 200 patients suffering from chronic cystitis in the relapse stage (group 1), 26 patients (13%) were included in the no-risk groups, 156 patients (78%) belonged to the risk group, 18 patients (9%) were included in the increased risk group. Out of 24 patients suffering from acute cystitis (group 2), 18 patients (75%) were in the risk group, and 19 patients (95%) of group 3 (20 patients suffering from chronic cystitis combined with chronic pyelonephritis) and 21 patients (95%) of group 4 (22 patients suffering from chronic cystitis combined with chronic salpingo-oophoritis) were in the increased risk group – the combination of the infectious syndrome with immunodeficient or allergic syndrome. Moreover, modifications in ranks were expressed to a minimum degree in patients of the no-risk group suffering from chronic cystitis in the relapse stage; modifications in ranks were expressed to an average degree in patients of the risk group suffering from chronic cystitis in the relapse stage; modifications in ranks were expressed to a large extent in patients of the increased risk group suffering from chronic cystitis in the relapse stage. The groups of patients intended for the complex examination were selected after determining the representativeness (Tables 1-3).

Table 1 demonstrated that proportion of the detection of basic clinical symptoms in patients of the no-risk, risk and increased risk groups ranged from 19, 30, 33% to 100%. Patients mostly manifested frequent urination, lower abdominal pains, cloudy urine with foul smell (84-100% of cases) and leukocyturia (in 58-72% of cases).

The dynamics of the bacteriologic findings (bacteriuria, E. coli culturing) in patients of three immunopatho-logic groups were equally extremely high (62-91%) and frequency of sterile samples was correspondingly low (6-9%).

The variations of hematologic inflammation markers by mean values were monotonous, but their frequency-response analysis revealed some peculiarities. Thus, the number of unchanged laboratory findings amounted to 67% in the patients of the no-risk group, 56% – in patients of the risk group, 33% – in patients of the increased risk group (P<0.05 for the latter group).

Identifying the signal tests summarized in FISD marked a qualitatively different nature of the laboratory findings. Hyperimmunoglobulinemia M combined with inhibition of phagocyte operative oxygen activity in the presence of T cells deficiency of the II-III degree was common in patients of the no-risk group - $IgM_3^+ NBT_{spont\ 2}^- T_2^-$;IgA deficiency, excessive IL-6 content of the maximal and moderate intensity was observed in patients of the risk group - $Tcytotoxic_3^+ IgA_2^- IL6_2^+$. The formula $NK_{cytotoxic\ 3}^+ T_{cytotoxic\ 3}^+ T_{helpers\ 3}^+$ confirmed the limited stimulation of the number of cytotoxic natural killers and lymphocytes and $T_{helpers}$ in patients of the increased risk group.

In addition to the abovementioned, the clinical stage of cystitis – primarily acute, secondary recurrent, its combinations with chronic pyelonephritis or salpingo-oophoritis – had an impact on the development of immunopathological syndromes and peculiarities of laboratory variations of patients' reactivity (Ditkoff et al. 2018, Gyaurgiyev et al. 2015).

Therefore, the pre-laboratory identification of risk groups based on the presence of immunopathological syndromes in case of cystitis can be considered as an indirect method of assessing anti-infectious resistance without any specific examination of patients (Bove et al. 2018, Cruz 2014, Jung et al. 2018).

Peculiarities of metabolic status in patients with chronic cystitis

An acute phase of chronic cystitis was found to be characterized by a valid increase of DC concentration from 34.6+-1.83 to 36.52+-1,47; KD – from 19.62+-0.77 to 25.01+-2.11; MDA – from 1.36+-0.06 to 1.7+-0.08 and BC – from 0.3+-0.012 to 0.37+-0.006. At the same time, the initial content of SOD and C was significantly stimulated from 1.14+=0.038 and 31.1+-1.43 to 1.0+-0,02 and 28,0+-0,9, which correlated with accumulation of vitamin E from 23.86+-0.71 to 15.8+-0.6 mcm/L and ST – from 44.52+-0.85 to 34.28+-28.7 mM/L. These findings prove the disrupting of the balance of the immune-aggressive factors – primary, secondary FRO products and enzymatic, non-enzymatic links of AOD.

Clinical laboratory effiacy of local and systemic immunotherapy of chronic cystitis in 7-10 days

The data obtained were summarized in Table 4. For discussing them, the frequency analysis revealing a risk of

Table 1. Clinical Laboratory Status of Patients with Chronic Cystitis in the Relapse Stage: Formalized Rank Evaluation of Groups with Various Immunologic Risks

Parameters	Patients of no-risk group (26)	Patients of risk group (156)	Patients of increased risk group (18)
Clinical parameters			
Frequent urination	26/100/1*	156/100/1*	18/100/1*
Urogenital incontinence	5/19/3*	131/84/1* **	16/89/1* **
Lower abdominal pains	23/88/1*	145/93/1*	18/100/1*
Cloudy urine	26/100/1*	156/100/1*	18/100/1*
Foul-smelling urine	14/53/2*	150/90/1* **	18/100/1* **
Subfebrile condition	9/35/2*	61/39/2*	8/44/2*
Intoxication	6/23/3*	61/39/2* **	10/56/2* **
Leukocyturia	15/58/2*	110/71/1*	13/72/1*
Hematuria	5/19/3*	47/30/3*	6/33/2*
% of deviation from the norm	55.0	72.3**	77.1* **
Bacteriologic parameters			
Bacteriuria	24/91/1*	142/91/1* **	17/94/1* **
E. coli	18/62/2 *	140/90/1*	16/89/1*
Other GN flora	2/8/3	2/1/3	1/6/3
Sterile samples	3/8/3	14/9/3	1/6/3
% of deviations from the norm	91.0	91.0	94.0
Routine hematologic parameters			
Leukocytosis	4/15/3	31/20/3*	6/33/2* **
Lymphopenia	1/4/3	14/9/3	4/22/3* **
Neutrophilia	5/20/3*	29/19/3*	4/22/3*
Monocytosis	2/8/3	5/3/3	4/22/2*
Accelerated ESR	1/4/3	4/3/3	1/6/3
% of deviations from the norm	10.2	16.6	21.0
Grouped immunologic parameters			
By mean values			
Total	50/2*	62/2*	73/1* **
Cellular	83/1*	75/1*	100/1* **
Humoral	67/1*	67/1*	67/1*
Phagocytic	50/2*	50/2*	50/2*
Cytokine	17/3*	50/2 * **	50/2* **
By frequency analysis			
Resulting	23/3*	39/2*	53/2* **
Σ of ranks	54/III	46/II	39/I
% of deviations from the norm	48.3	57.2	65.5**
Mean % of deviations	43.5	56.6	59.0**

Note: Σ – sum of ranks (a number of patients/ % of deviations from the norm/rank); 1 – reliable significant (deviations > 66% of parameters), 2 – reliable mean (33-66%), 3 – insignificant (<33%); *- validity of deviations from the norm when P<0.05; **- validity of deviations from the parameters of patients of the no-risk group; the rest see above.

pathology development of individual tests from the target level in patients' population was used.

As Table 4 shows, 30-100% changes of the urine syndrome parameters and 39-93% changes of the intoxication syndrome parameters were registered in patients in the acute stage of chronic cystitis; positive bacteriologic tests were revealed in 90-91% of cases, sterile samples – in 9% of cases; variations of routine hematological findings of inflammation markers amounted to 3-25%, which corresponded to pathological findings of the 75% of grouped cellular, 67% of humoral, 50% of phagocytic and cytokine parameters.

Table 2. Actual Deviations of Laboratory Parameters from the Standard Level in Patients with Cystitis

Parameters	Group 1			Group 2	Group 3	Group 4
	No-risk group	Risk group	Increased risk group	Risk group	Increased risk group	Increased risk group
Cellular parameters						
T	-	-	-	-	-	
T-helpers	+	-	-	-	-	-
T-cytotoxic	-	-	-		-	+
T-regulatory				+	-	-
T-activated	-	-	-	+	+	+
NK$_{T-dependent}$		+	-	+	+	+
NK$_{regulatory}$	+	+	+	+	+	+
NK$_{cytotoxic}$			+	+	+	
Humoral parameters						
B	+	+	+	+	+	
IgM	+	+		+	+	+
IgG			+	+	+	-
IgA		-	-	+	+	-
Circulating immune complexes (CIC)	+	-	+	+	+	+
Medium weight molecules (MWM)	+				+	+
Phagocytic parameters						
CD11b				+		-
CD18						
Phagocytic index (PhI)	+	-	-	+	+	-
Phagocytic number (PhN)	+	-	-	+	+	-
Nitro Blue Tetrozolium spontaneous (NBT$_{spont}$)	-		-	-	-	-
Nitro Blue Tetrozolium activated (NBT$_{activ}$)		-	-		-	-
Cytokine parameters						
IL2					-	
IL4				-	-	-
IL6		+	+		+	+
IL8	+	+		+	+	+
IL10						
Tumor necrosis factor (TNF)		+			+	+

Note: +/- reliable deviations of parameters from the norm, P< 0.05.

Efficacy of the conventional therapy of chronic cystitis

Significant normalization of clinical parameters was achieved in patients 7-10 days after the administered standard treatment. Frequent urination, urge urine incontinence, cloudy foul-smelling urine, lower abdominal pains, leukocyturia, terminal hematuria were registered in 16-21% of cases, and subfebrile condition, intoxication were completely eliminated. The total percentage of deviations from the norm before and after treatment made up 72.7 and 11.1%, with the 6.5-time difference. Moreover, bacteremia in the urine with E. coli monoculturing decreased from 90-91% to 25%, and the number of sterile samples consistently increased to 75%; on average, the normalizing dynamics of bacteriologic parameters increased 3.6 times.

Leukocytosis, lymphopenia, neutrophilia persisted in 16% of patients; monocytosis and accelerated ESR were registered in isolated cases with unreliable 1.2-time variations of hematologic parameters.

The following fact should be taken into consideration when assessing the variations of immunologic parameters: 7-10 days appeared to be a non-optimal period of examination, which was evidently insufficient to develop rehabilitation mechanisms. From this perspective, the parameters revealing regularities of reaction in patients with cystitis were grouped in total and by separate components of the immune system. Resulting normalizing immunotropic effect of the conventional therapy of chronic cystitis in the relapse stage was low, since, in terms of quantity, the number of the modified tests

Table 3. Interpretation of the Immune Status Depending on the Risk Group in Patients with Immune Cystitis

Disorder	Group of risk	Grouped parameters				Sum of ranks	Devia-tions	Key parameters	
		C	H	Ph	Cy			T:B:N	FISD
Acute cystitis	Risk group	1	1	2	3	7	IV	2:1:3	$T_{cytotoxuc\ 3}^{*}IgM_{3}^{*}MWM_{2}^{*}$
Chronic cystitis in the relapse stage	No-risk group	2	1	2	3	8	V		$IgM_{3}^{+}NBT_{spont\ 2}^{-}T_{3}^{-}$
	Risk group	1	1	2	2	6	III	2:2:2	$T_{cytotoxic\ 3}^{+}IgA_{2}^{-}IL6^{+}$
	Increased risk group	1	1	1	2	5	II		$NK_{cytotoxic\ 3}^{+}T_{cytotoxic\ 3}^{+}Thelpers_{3}^{+}$
Chronic cystitis combined with chronic pyelonephritis	Increased risk group	1	1	1	1	4	I	2:2:2	$CIC_{3}^{*}T_{3}^{*}PhN_{3}^{-}$
Chronic cystitis combined with chronic salpingo-oophoritis	Increased risk group	1	1	1	1	4	I	1:2:3	$Tregulatory_{2}^{*}NK_{regulatory\ 2}^{*}MWM_{3}^{*}$

Note: 1, 2 ranks – reliable deviations from the norm level in 66-100% and 33-66% of patients, 3 – unreliable - < 33%; C, H, Ph, Cy – cellular, humoral, phagocytic, cytokine parameters; T:B:N – distribution of key tests modifications into T-, B-dependent and Non-specified links of the immunity in ranks.

Table 4. Clinical Laboratory Effects of Differentiated Immunotherapy of Chronic Cystitis in 7-10 Days – 3-4 Months

Parameter	Variants of treatment								
	Back-ground	Conven-tional therapy	+Kf	+Sl	+If	+Gl	+Sl+If	Conven-tional therapy	Sl+If
			7-10 days					3-4 months	
% of clinical parameters									
Frequent urination	100**	16* **	16* **	0* ***	8* ***	12*	0* ***	75* **	24* ** ***
Urge urine incontinence	83**	16* **	12*	8*	0* ***	0* ***	0* ***	50* **	15* ***
Lower abdominal pains	93**	12*	12*	8*	8*	4*	4*	65* **	10* ***
Cloudy urine	100**	16* **	8*	0* ***	0* ***	4*	0* ***	75* **	0* ***
Foul-smelling urine	96**	12*	0*	0*	0*	0*	0*	75* **	0* ***
Subfebrile condition	39**	0*	0*	0*	0*	0*	0*	25* **	0* ***
Intoxication	39**	0*	0*	0*	0*	0*	0*	30* **	0* ***
Leukocyturia	71**	12*	4 *	4*	0*	0*	0*	50* **	0* ***
Hematuria	30**	16	0*	0* ***	0* ***	0* ***	0* ***	35**	0 * ***
% of bacteriological parameters									
Bacterimia	91**	25* **	4* ***	4* ***	4* ***	0 * ***	0* ***	9/45* **	25* ** ***
E.coli	90**	25* **	4* ***	4* ***	4* ***	4* ***	0* ***	9/45* **	25* ** ***
Unidentified GN flora	3	6	0	0	0	0	0	0	0
Sterile samples	19	75* **	92* ** ***	96* ** ***	92* ** ***	96* ** ***	96* ** ***	9/45* **	75* ** ***
% of routine hematologic parameters									
Leukocytosis	20**	16**	0* ***	0* ***	0* ***	0* ***	0* ***	25**	0 * ***
Lymphopenia	9	16**	12	16**	8	6	0***	19**	10

Table 4. (continued)

Parameter	Variants of treatment								
	Back-ground	Conven-tional therapy	+Kf	+Sl	+If	+Gl	+Sl+If	Conven-tional therapy	Sl+If
				7-10 days				3-4 months	
Neutrophilia	19**	16**	4	0* ***	4	12	0* ***	15	0*
Monocytosis	2	12	4	8	12	20**	20**	0	25* ** ***
ESR	1	8	0	4	4	0	0	5	0
	% of grouped immunologic parameters								
Total	62	62	46* ***	31* ***	38* ***	50*	27* ***	75	31* ***
Cellular	75	63	38* ***	50*	13* ***	50*	25* ***	83	25* ***
Humoral	67	67	50* ***	67*	50* ***	67	17* ***	67	17* ***
Phagocytic	50	50	17* ***	0* ***	13* ***	0* ***	17* ***	67*	33* ***
Cytokine	50	67*	83* ***	0* ***	83* ***	83* ***	50* ***	67*	33* ***
% of deviations from the norm	61.8	61.8	46.8	29.6	39.5	50.0	7.1	45.6	13.0

Note: *- deviations from the background, ** - deviations from the norm, *** - deviations from the conventional therapy, $P<0.05$.

was reported to be equal to the initial one – 16 and 16 (61.5%).

In terms of quality, the treated patients manifested suppression of the cellular immunity, accumulation of B-cells, dysimmunoglobulinemia M, G, A, a reduced absorptive and metabolic capacity of phagocytes, disbalance of pro- and anti-inflammatory cytokines.

As a result, implementing the conventional non-immunotropic treatment of chronic cystitis in the early relapse stage, on 7-10 days, promoted the high-grade remission of the disease with retaining the clinical symptoms in 11.1% of cases, modified bacteriological parameters in 25% of cases, routine hematologic parameters in 13.6% of cases, immunologic parameters in 61.8% of cases.

Efficacy of the local immunotherapy of chronic cystitis in the relapse stage with application of kipferon and superlimf

Kipferon – a complex of immune globulins of the main classes in combination with recombinant human interferon – was selected as a local modulator. It is usually applied in immunodeficient conditions, supperative-inflammatory processes in urogenital organs, etc. (Strel'tsova et al. 2013).

A complex treatment with kipferon in patients suffering from the given disorder, who had 10-30% of modified clinical parameters before treatment, provided the following results: subfebrile condition and general intoxication were completely eliminated; lower abdominal pains, foul-smelling urine, leukocyturia remained in 12% of cases; and frequent urination, hematuria remained in 16% of cases. In addition, a period of hospitalization significantly reduced with using kipferon –
from 6.0+-0.5 days to 4.9+-1.0 days, P < 0.05.

Additional administration of Kf to patients with the given disorder resulted in the reduction of the initial bacteriuria and E. coli culturing from 91-90% to 25%, and an increase in urine sterility from 9 to 92%.

Dynamics of routine hematologic parameters of inflammation tended to normalize, but appeared insignificant.

The identification of the final normalizing immunotropic effect from the traditional therapy combined with kipferon provided reliable, but not considerable effect, since the proportion of parameter deviation decreased from 61.5 to 46.8%.

In terms of quality, the modulator provided accumulation of T cytotoxic suppressors combined with a decreased level of main populations of killer cells, with stimulation of the B-cells content, immune globulins of two classes against the background of phagocytosis inactivity, hyperproduction of anti-inflammatory interleukins 2, 6, 8 and a decrease in tumor necrosis factor alpha (TNF-alpha).

Superlimf is a natural complex of immune peptides with the activity of certain cytokines. The preparation stimulates leukocytes and phagocytosis, tissue regeneration, and reduces intensity of inflammation. It is applied in treatment of secondary immunodeficient conditions, supperative wounds, and trophic ulcers (Daniels et al. 2018, Neymark et al. 2016).

As Table 4 demonstrates, a clinical effect of superlimf in combination with the conventional therapy of cystitis proved to be rather significant, since 6 out of 9 studied parameters – frequent urination, cloudy urine, foul-smelling urine, subfebrile condition, intoxication, hematuria – were normalized to zero. Leukocyturia persisted in 4% of cases, urge urine incontinence and lower abdominal pains persisted in 8% of cases. The average proportion of deviations of clinical parameters from the norm amounted

to 2.2%, which was reported to be 33 times lower than before the treatment – 72.7%. This considerable effect of the complex treatment resulted in a reduced period of hospitalization of patients with the disorder in question to 4.5 +-1.0 days.

The effect of superlimf immunotherapy on bacteriologic parameters of patients was similarly significant, indicating a decrease in the initial bacteriuria, mainly with E. coli monoculture, from 90-91% to 4% (a 22.8-time deviation); the number of sterile samples accordingly increased from 9 to 96%, a 10-time increase.

Normalization of the routine hematologic parameters of inflammation was less pronounced. Leukocytosis persisted in 16% of cases, neutrophilia – in 8% of cases, monocytosis – in 4% of cases; limphopenia and ESR were eliminated to 0%. However, it should be highlighted that the initial deviation of these parameters from the norm was low, from 1 to 20%. Nevertheless, in average, the percentage of deviations from the norm was insignificant and amounted to 5.6%.

Nonetheless, the capacity of superlimf to cause qualitative deviations of immunologic parameters from the initial level was relevant – 6 tests out of 26 (21.9%). As a result, the deviations of the parameters from the norm – 29.6% - were statistically significant, P<0.05.

The abovementioned qualitative changes were combined with disbalance of cellular parameters, standard reaction of the humoral arm in the form of an increased concentration of B-lymphocytes, IgM, IgG, a decreased number of the immunoglobulin A with no variations of phagocytic and cytokine parameters.

Special attention should be paid to the fact that efficacy of the local immunomodulator effect firstly on the clinical and bacteriologic, and then – on routine hematologic and immunologic parameters, reduced gradually.

Thus, immunotherapy with additional application of the local immunity modulators kipferon and superlimf in patients with chronic cystitis decreased the proportion of deviations from the norm:
- of clinical parameters – 12.5 and 32.9 times (from 72.3 to 5.8 and 2.2%, respectively);
- of bacteriologic parameters – 17.1 and 22.7 times (from 90.7 to 5.3 and 4.0%);
- of routine hematologic parameters – 3.5 and 3.0 times (from 16.6 to 4.8 and 5.6%);
- of immunologic parameters – 5.5 and 6.2 times (from 55.6 to 10.2 and 9.0%).

Overall, high average clinical laboratory normalizing efficacy of one conventional treatment – 2.4 times –was exceeded 5.5 and 6.2 times.

Efficacy of systemic immunotherapy of chronic cystitis with application of imunofan and galavit

Imunofan is a synthetic thymomimetic drug, hexapeptide with immunoregulating, detoxic, hepaprotective, metabolic characteristics, capable of inactivating lipid peroxidation, activating the antioxidant system, as well as cellular

and humoral immunity, and suppressing excessive inflammation (Jung et al. 2018, Keagy 2018).

The performed study demonstrated that if additionally administered to patients resulted in the normalization of 5 out of 6 symptoms of the urine syndrome: urge urine incontinence, cloudy and foul-smelling urine, leukocyturia and hematuria. However, frequent urination persisted in 8% of patients. Two symptoms characterizing the intoxication syndrome – subfebrile condition and general malaise – were completely eliminated. Frequent urination and lower abdominal pains were eventually detected in 8% of cases. The duration of hospitalization was 5.1±0.9 days.

The examination of the urine bacteriologic parameters showed a decrease in the initial bacteriuria and pathognomonic E. coli culturing from 90-91% to 4%. Thus, the number of sterile samples increased from 9 to 92%.

The deviation of routine hematologic markers of inflammation from the baseline parameters was insignificant, but tended to decrease. For example, the baseline parameters of leukocytosis fell from 20% to 8%, and the baseline parameters of neutrophilia fell from 19% to 12%. Monocytosis, accelerated ESR were detected in isolated cases before and after the treatment. On average, the total proportion of hematologic parameters in treated patients significantly decreased from 16.6 to 4.9% (3.4-time difference).

The deviation of immunologic parameters from the baseline ones under the influence of the conventional therapy combined with imunofan modulator therapy significantly changed in 34.6% of tests; the corresponding parameter made up 61.8 and 39.5% of the norm, P <0.05.

It the patients of this group discharged from the hospital, inactivity of T-dependent parameters, accumulation of B-cells, CIC, a decrease in IgA formation, occasional accumulation of cells with CD11b marker in combination with IL6, IL8 hyperproduction, IL4 and TNF-alpha hypoformation were detected.

Galavit was selected as the second modulator of systemic immunity. This preparation - aminodioxotetrahydrophtalasinedione sodium – is characterized by anti-inflammatory, antioxidant, immunomodulating properties, regulates pro- and anti-inflammatory cytokines, activates macrophages, granulocytes, natural killers, interferons and is applied in infectious, inflammatory, urogenital pathologies of pelvic organs (Dellis and Papatsoris 2018, Lai et al. 2014).

As Table 4 demonstrates, application of galavit provided a manifold decrease in initially prevailing (in 83 out of 100% of cases) major symptoms of the urine syndrome – frequent urination, urge urine incontinence, claudy and foul-smelling urine, lower abdominal pains – to 0-4-12%. Moreover, subfebrile condition, intoxication, leukocyturia, hematuria decreased from 30-71% to zero. On average, the proportion of deviation of clinical parameters from the norm was 72.3 and 2.2%. The duration of hospitalization of patients with chronic cystitis in the relapse stage treated in complex with galavit was 6.0±0.5 and 4.3±0.8 days, P <0.05.

Highly positive results were obtained when studying dynamics of bacteriologic parameters in patients.The baseline parameters of bacteriuria decreased from 91% to zero, and E. coli culturing – from 90% to 4%. With that,, the proportion of sterile urine samples increased from 9 to 96%.

In 5 investigated hematologic parameters of leukocytosis inflammation, the proportion of detection decreased from 20 to 6%. Though the variations of other laboratory parameters were not so impressive, the proportion of deviations of parameters from the norm decreased from 16.6% to 5.1% on average.

An immunotropic effect of galavit in a frontal descriptive analysis was the following: mobile effect of the preparation was expressed in relevant deviation of the parameters from the baseline – by 42.3%. With that, 50% of tests deviated from the norm. The analysis of qualitative peculiarities stated the excess amount of T cytotoxic, NK, the deficiency of T-helpers and T-regulatory, irritation of B-link by Ig of two main classes, MWM and cytokine parameters – IL2, 4, 6, 8 combined with insufficiency of anti-inflammatory TNF.

Thus, immunotherapy with additional application of the local immunity modulators imunofan and galavit in patients with chronic cystitis decreased the proportion of deviations from the norm 7-10 days later:
  – of clinical parameters – 40.2 and 32.9 times (from 72.3 to 1.8 and 2.2%, respectively);
  – of bacteriologic parameters – 17.1 and 33.6 times (from 90.7 to 5.3 and 2.7%);
  – of routine hematologic parameters – 3.4 and 3.2 times (from 16.6 to 4.9 and 5.1%);
  – of immunologic parameters – 1.6 and 1.2 times (from 61.6 to 39.3 and 50.0%).

Overall, high average clinical laboratory normalizing efficacy of non-immunotropic treatment – 2.4 times –was exceeded 5.2 and 4.3 times.

Efficacy of the combined immunotherapy of chronic cystitis with application of superlimf and imunofan

A preliminary study demonstrated high capacity of the conventional non-immunotropic treatment of chronic cystitis in the relapse period to correct clinical and bacteriologic parameters, but not routine hematologic and immunologic ones. Additional administration of local and systemic immunostomulators relevantly resulted in the normalization of not only clinical and bacteriologic, but also hematologic and immunologic parameters. That is why some patients were grouped to be treated complexly with Sl with If (Gyaurgiyev et al. 2015, Kapral et al. 2018, Tyuzikov et al. 2018).

The data obtained indicated a practically limited clinical effect of the combined immunotherapy. Complete elimination of frequent urination, cloudy and foul-smelling urine (the baseline parameters 100 – 96%), urge urine incontinence (the baseline parameters – 83%), subfebrile condition and intoxication (the baseline parameters – 39%), terminal hematuria (the baseline parameters

– 30%) was obtained in all patients. Only 4% of patients treated with a complex therapy still had lower abdominal pains and leukocyturia.

The bacteriological data demonstrated that urine bacteriuria with E. coli monoculturing persisted only in one patient of 25; accordinly, the number f sterile samples of diagnostic material increased from 9% to 96%.

Initially low detection of hematologic markers of inflammation – leukocytosis, limphopenia, neutrophilia, accelerated ESR – decreased after application of two modulators to isolated cases; monocytosis was only registered in 20% of cases after the treatment.

A mobile effect of the combination of immunocorrectors on patients' immunologic parameters was significant compared to the baseline and included 14 parameters – 54% of all investigated tests. Correspondingly, the normalizing effect of the modulators turned out to be maximal. As a result, the cellular and humoral parameters returned to normal, whwereas the phagocytic and cytokine ones did not.

Overall, general proportion of the modified clinical laboratory parameters decreased 8.2 times 7-10 days after administration of the complex of correctors; which was significantly higher than the effect of one conventional treatment – 2.4 times.

Efficacy of the conventional treatment and combined immunotherapy of chronic cystitis with superlimf and imunofan in 3-4 months

As Table 4 demonstrates, the proportion of the modified parameters in the group of the controlled treatment were as follows (the baseline – after 7-10 days – after 3-4 months): the percentage of frequent urination was 100-16-75%, of urine incontinence – 83-16-50%, of pain syndrome – 93-12-65%, of cloudy and foul smelling urine – (100-96%) – (16-12%) – 75%. Completely eliminated subfebrile condition and intoxication increased to 25-30% in the extended period, leukocyturia and hematuria grew from 12-16 to 50-35%.

Similar parameters were obtained when assessing variations of bacteriologic laboratory parameters. Thus, bacteriuria and E. coli culturing increased from the baseline parameters (90-91%) to 25% obtained after 7-10 days and to 45% after 3-4 months. Variations of sterile samples amounted to 9% – 75% – 45%, respectively. Leukocytosis, limphopenia and neutrophilia were registered within the limits 25%-19%-15%. Overall, on average general frequency of deviations of bacteriologic, routine, hematologic tests from the norm approached to the baseline parameters observed before treatment.

It should be noted that an immunotropic effect of the conventional treatment of chronic cystitis after 3-4 months was as insignificant as at the earlier period. Apparently, assessment of these reactions after 7-10 days was too early, and after 3-4 months – too late. For example, a normalizing effect of the conventional treatment at the later period was sufficiently low, since relevant deviation of 17 clinical laboratory parameters out of 26 studied

parameters (65.4%) was was recorded, compared to the baseline – 16 (61.5%) - and 7-10 days after treatment – 16 (61.5%).

Due to the fact that the positive clinico-bacteriological effect of the conventional therapy wore off 3-4 months after the treatment, disease recurrence was observed (Gelashvili et al. 2014, Kurilovich 2017).

Analysis of efficacy of the immunotherapy with the combination of superlimf and imunofan in patients with acute cystitis in the relapse period demonstrated that after 3-4 months the deviation from the norm was registered only in one out of 9 clinical parameters.

Practically similar results were obtained when investigating patients' bacteriologic parameters. Application of the combination Sl+If resulted in a decrease in systemic bacteremia, E. coli culturing from 91-90% to 45% and 25%, and an increase in the proportion of sterile samples from 9% to 45% and 75% compared to the baseline and the level of one conventional treatment after 3-4 months.

Studying the variations of hematologic evidences of inflammation revealed certain monotony in this period. However, mean values of the deviations – 12.8 and 7% – tended to normalize.

The results of immunotropic effect of the conventional treatment combined with modulators appeared to be insignificant after 3-4 months, resulting in the relevant variations of 6 tests out of 26 (21.3%) compared to the

parameters obtained after 7-10 days – 14 tests (54%). However, resulting mean values of the clinical laboratory parameters of patients from the control and experimental groups made up 45.6% and 13.0% of the norm at the later period. Therefore, a normalizing effect of the immunotherapy at the later period was lower than that in the acute period, but still significant to prevent relapse of the disease.

Key targets of the differentiated immunotherapy of chronic cystitis

The key components of target formulas of individual immunotropic preparations were defined, and their individuality was stated: depending on the set and the order of arrangement, on the vector and degree of intensity of deviations (Table 5). Thus, FTI (the formula of targets of immunocorrection) of one conventional treatment included $NBT_{spont+3}$ $NK_{cytotoxic-2}$ TNF_{+3}. The impact of the conventional treatment combined with Kf distributed into TNF, CIC, T_{activ} lymphocytes; combined with Sl – into IL4, T_{cells}, PhI; combined with If – into T-lymphocytes, $T_{helpers}$, MWM; combined with Gl – into NBT_{spont}, NBT_{active}, IL4; and combined with Sl+If – into subpopulations of natural killers.

The determined individuality of mechanisms of action of the complex treatment depended on the immunotropic

Table 5. Signal Parameters and Their Correlative Links in Patients with Chronic Cystitis after Differentiated Treatment

Key formulas	Therapeutical variations					
	Conventional therapy	+Kf	+Sl	+If	+Gl	+Sl+If
After 7-10 days						
$FISD_{baseline}$			$T_{cytotoxic}^+{}_3$ $IgA^-{}_2$ $IL6^+{}_2$			
FTI	$NBT_{spont}^+{}_3$ $NK_{cytotoxic}^-{}_2$ $TNF^+{}_3$	$TNF^-{}_3$ $CIC^-{}_2$ $T_{activ}^+{}_2$	$IL4^+{}_3$ $T^+{}_2$ $PhI^+{}_2$	$T^+{}_3$ $T_{helpers}^+{}_3$ $MWM^-{}_3$	$NBT_{spont}^+{}_2$ $NBT_{activ}^+{}_3$ $IL4^+{}_3$	$NK_{T\text{-}depen}^+{}_3$ $NK_{cytotoxic}^+{}_3$ $NK_{regulat}^+{}_3$
FTI_{prop}		$T^+{}_2$ $TNF^-{}_3$ $IL4^+{}_3$	$PhN^+{}_3$ $PhI^+{}_2$ $IL4^+{}_3$	$T_{cytotoxic}^+{}_3$ $T_{helpers}^+{}_3$ $T_{regulat}^+{}_3$	$IgA^+{}_3$ $NK_{cytotoxic}^+{}_2$ $TNF^-{}_3$	$T^+{}_3$ $T_{activ}^+{}_3$ $NBT_{activ}^+{}_2$
$FISD_{im}$	$IgG^+{}_3$ $CD18^+{}_3$ $PhN^+{}_3$	$NK_{regulat}^+{}_3$ $IL2^+{}_2$ $IgG^+{}_3$	$NK_{cytotoxic}^+{}_3$ $T_{cytotixic}^+{}_3$ $IgG^+{}_3$	$CD11в^+{}_3$ $B^+{}_3$ $IL8^+{}_2$	$T_{cytotoxic}^+{}_3$ $IgM^+{}_3$ $IgG^+{}_3$	$T_{activ}^+{}_2$ $B^+{}_2$ $CD11в^+{}_3$
After 3-4 months						
FTI	$NK_{regulat}^-{}_2$ $IL10^+{}_2$ $T^-{}_2$					$T_{activ}^+{}_3$ $IgG^-{}_3$ $IL6^-{}_2$
FTI_{prop}						$T^+{}_3$ $T_{helpers}^+{}_3$ $T_{activ}^+{}_3$
$FISD_{im}$	$NK_{cytotoxic}^-{}_3$ $IgM^+{}_2$ $T_{regulat}^-{}_2$					$IgA^-{}_2$ $T_{activ}^+{}_2$ $IgG^+{}_3$

Note: *- deviations from the background, ** - deviations from the norm, *** - deviations from the conventional therapy, P<0.05.

properties of the conventional therapy and properties of correctors. A "proper" effect of modulators was detected using a special mathematic method (Zemskov et al. 2008). For example, FTI of the complex of the basic therapy combined with Gl included $NBT_{spont+2}$ $NBT^+_{activ\ 3}$ $IL4^+_3$, and one modulator (FTI_{prop}) – absolutely different parameters - IgA^+_3 $NK^+_{cytotoxic\ 2}$ TNF^-_3.

Correlation of signal parameters of the immune disorders in the treatment of chronic cystitis

Strong correlative associations of immunologic parameters with other parameters of laboratory status marked tension in the immune system with the following interpretation: the more associations are revealed, the higher is the optimality of functioning and, consequently, the efficacy of treatment (Zemskov et al. 2016).

The data obtained evidenced that coordinated association of laboratory parameters in patients with cystitis was lower than that in healthy people; the number of strong associations of basic parameters of FISD during the treatment increased compared with the baseline; and in case of additional application of modulators – even compared to application of only conventional preparations. Moreover, various immunotropic preparations resulted in differentiated modulation of tension in the immune system (Malik et al. 2018).

Detection of significant associations between immunologic FISD tests ($T_{helpers+3}$ $IgA_{-2}IL6_{+2}$) and metabolic stress parameters in patients was especially important. Accumulation of T cytotoxic suppressors positively correlated with the primary product of lipid and protein oxidation – diene conjugates, and an increased concentration in anti-inflammatory IL6 negatively correlated with enzymatic and non-enzymatic factors (vitamin E and systemic thiols) of an antioxidant defense. The above makes it possible to assume the presence of a certain hypothetic link between immunologic and metabolic parameters in patients with chronic cystitis.

Laboratory parameters to select optimal immunotherapeutic options of chronic cystitis

An inversion analysis of calculated FTI was applied for tailor-made selection of optimal modulators (Zemskov et al. 2016, Zemskov et al. 2017). The principle of the method is as follows: if, for example, according to FTI – $NBT_{spont\ 2}^+$ $NBT_{activ\ 3}^+$ $IL4^+_3$ – galavit determines activation of the NBT_{spont} and NBT_{activ} of 2-3 degree and the limited formation of IL4, thus, this modulator will be efficient in the reduction of the indicated degree of indicators.

It was stated that one conventional treatment of patients with chronic cystitis may be administered when NBT_{spont} > 14.1%, $NK_{cytotoxic}$ – 0.06-0.08 *10^9/l, TNF > 0.32 pcg/ml; kipferon – TNF<0.06 pcg/ml, CIC – 9.1-18.3 RU, T_{activ}-0.16-0.82*10^9/l; superlimf – IL4>32.6 pcg/ml, T -2.0-2.3 *10^9/l, PhI – 96.6-129,7%; imunofan – T>2.5*10^9/l, T_{helper}-1.46-1.8*10^9/l , MWM<1.9 RU; galavit – NBT_{spont}

-11.3-14.1%, NBT_{activ}> 37.5%, IL4 > 32.6 pcg/ml; super-limf+ imunofan NK_T >0.9*10^9/l, $NK_{cytotoxic}$> 0.2*10^9/l, $NK_{regulat}$>0.59*10^9/l.

Comparative efficacy of differentiated immunotherapy of chronic cystitis in formalized evaluation

The results of the overall evaluation of the clinical laboratory efficacy of differentiated immunotherapy are given in Table 4.

The data obtained evidenced that various immunotherapeutic options of chronic cystitis cause a differentiated action on the patients' clinical, bacteriologic, hematologic and immunologic parameters. As a result, the overall decreasing range of treatment efficacy after 7-10 days was as follows: Sl+If, Sl, Kf, If, Gl, ConvTh (conventional therapy); after 3-4 months – ConvTh, ConvTh+Sl+If.

Conclusions

1. Chronic cystitis in the relapse stage is accompanied by the underlying formation of immunopathologic syndromes; which makes it possible to include the given patients into the risk group. This is accompanied by the development of typical clinical symptoms in 72.3% of cases, deviation of bacteriologic parameters in 90.7% of cases, deviation of routine hematologic parameters in 16.6% of cases, deviation of immunologic parameters in 57.8% of cases. The key components of the immune disorders in the presence of disbalance of the primary and secondary, enzymatic and non-enzymatic mechanisms of oxidative stress are formalized in the formula.

2. Conventional non-immunotropic therapy of chronic cystitis in the relapse stage results in a significant decrease in deviations from the norm after 7-10 days, as regards the incidence:
   – of clinical symptoms – from 72.3 to 11.1%, (6.5 times);
   – of biological parameters markers – from 90.7 to 25.0% (3.6 times);
   – of routine hematologic parameters – 16.6 and 12.8% (insignificantly);
   – of immunologic parameters – 61.8-61.8% (insignificantly).

   The positive clinical bacteriologic effect of the conventional treatment completely wears off after 3-4 months; which results in the relapse of the disease.

3. Additional immunotherapy with modulators of the local immunity – kipferon and superlimf – administered to patients with chronic cystitis decreases the proportion of the deviations from the norm after 7-10 days:
   – of clinical parameters - 12.5 and 32.9 times;
   – of bacteriologic parameters – 17.1 and 22.7;
   – of routine hematologic parameters – 3.5 and 3.0 times;
   – of immunologic parameters – 5.5 and 6.2 times.

Overall, high average clinical laboratory normalizing efficacy of one conventional treatment – 2.4 times – was exceeded 5.6 and 6.2 times.

4. Additional immunotherapy with modulators of the local immunity – imunofan and galavit – administered to patients with chronic cystitis decreases the proportion of the deviations from the norm after 7-10 days:
   - of clinical parameters - 40.2 and 32.9 times;
   - of bacteriologic parameters – 17.1 and 33.6 times;
   - of routine hematologic parameters – 3.4 and 3.2 times;
   - of immunologic parameters – 1.6 and 1.2 times.

   Overall,high average clinical laboratory normalizing activity of non-immunotropic treatment – 2.4 times – was exceeded 3.4 and 2.2 times.

5. A normalizing clinical laboratory effect of the combined immunotherapy of chronic cystitis in the relapse stage with superlimf and imunofan is reported to be lower at the later period – after 3-4 months - compared with the parameters obtained after 7-10 days. However, this effect is sufficient enough to prevent the relapse of the disease. On average, the proportion of deviations from the norm of all tests at the indicated periods decreased from 53.8% to 26.1% and 14.2%, the difference being 2.1-3.8 times.

6. Six options of the immunotherapy of chronic cystitis in the relapse stage implement various mechanisms of action on patients'clinical-laboratory parameters, their correlative links dependant on the conventional treatment given, the types of modulators and their combinations, the duration of examining patients, the following range of activity of the drugs is offered – Sl+If, Sl, Kf, If, Gl, ConvTh.

Conflicts of interest

The authors have no conflict of interest to declare.

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