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FEATURES OF CHANGES IN THE INDICATORS OF T-CELL IMMUNITY IN PATIENTS WITH DIFFERENT CONTROLLING OF BRONCHIAL ASTHMA AND THEIR PROGNOSTIC VALUE

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Abstract. *The aim:* to determine the prognostic assessment of T-cell immunity changes which are based on the study of their features in bronchial asthma (BA) patients with its different controllability. *Materials and methods.* 133 BA patients were examined: 11 patients with controlled, 63 patients with partially controlled and 59 patients with uncontrolled BA. The control group consisted of 36 volunteers. The content of leukocytes, the relative and absolute quantity of lymphocytes, pan-T cells, T-helper cells, cytotoxic T-lymphocytes, immunoregulatory index (IRI), T-cell proliferative response to phytohemagglutinin (PHA) in lymphocyte blast transformation reaction (LBTR), as well as the character and frequency of these indicators changes were determined. *Results*. In controlled BA a decrease in the content of pan-T and T-helper cells, an increase in the quantity of cytotoxic T-lymphocytes were detected, which in 44.4 % of cases were resulted in a decrease of IRI. In the greater part of patients with partial BA control the reference and elevated T-helper content, a decrease in the quantity of cytotoxic T-cells and IRI were found, which are distinctive signs of the breakdown of adaptive immunological mechanisms. In patients with uncontrolled BA increased T-cell content, a decreased cytotoxic T-lymphocytes quantity and increased IRI were found, which indicated immunological disadaptation. The suppression of LBTR to PHA was recorded in only 24.6 % of these patients, which may be an indirect sign of steroid resistance. *Conclusions*. Individual changes in the indices of T-cell immunity can be used to predict the controlled or uncontrolled course of BA. These approaches make it possible to revise the treatment plan for patients in advance and prevent them from losing control of the disease.

Key words: bronchial asthma, controllability, T-lymphocytes, prognostication.

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ОСОБЛИВОСТІ ЗМІН ПОКАЗНИКІВ Т-СИСТЕМИ ІМУНІТЕТУ У ХВОРИХ З РІЗНОЮ КОНТРОЛЬОВАНІСТЮ БРОНХІАЛЬНОЇ АСТМИ ТА ЇХ ПРОГНОСТИЧНЕ ЗНАЧЕННЯ

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Резюме. *Мета:* з'ясування прогностичного значення змін Т-системи імунітету на підставі вивчення їх особливостей у хворих на бронхіальну астму (БА) з різною її контрольованістю. *Матеріали та методи*. Обстежено 133 хворих на БА: 11 хворих з контрольованою, 63 із хворих частково контрольованою та 59 хворих із неконтрольованою БА. Групу контролю склали 36 волонтерів. Визначали вміст лейкоцитів, відносну і абсолютну кількість лімфоцитів, пан-Т-клітин, Т-хелперів, цитотоксичних Т-лімфоцитів, імунорегуляторний індекс (IPI), проліфера-

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тивну відповідь Т-клітин на фітогемаглютинін (ФГА) в реакції бласттрансформації (РБТЛ), а також характер і частоту змін цих показників. *Результати.* При контрольованій БА виявлено зменшення кількості пан-Т-клітин і Т-хелперів, збільшення числа цитотоксичних Т-лімфоцитів, що в 44,4 % випадків зумовило зменшення ІРІ. У більшості хворих з частковим контролем БА визначалися референтний і підвищений вміст Т-хелперів, зменшення кількості цитотоксичних Т-клітин і ІРІ, що є характерними ознаками зриву адаптаційних імунологічних механізмів. При неконтрольованій БА виявлялося підвищення вмісту Т-клітин, зменшення кількості цитотоксичних Т-лімфоцитів і зростання ІРІ, що свідчило про імунологічну дезадаптацію. Пригнічення проліферативної відповіді Т-клітин на ФГА було зафіксовано тільки у 24,6 % пацієнтів, що може бути непрямою ознакою стероїдної резистентності. *Висновки.* Індивідуальні зміни показників Т-системи імунітету можуть використовуватися для прогнозування контрольованого або неконтрольованого перебігу БА. Ці підходи дозволяють заздалегідь переглянути схему лікування хворих і попередити втрату ними контролю над хворобою.
Ключові слова: бронхіальна астма, Т-система імунітету, контрольованість.

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ОСОБЕННОСТИ ИЗМЕНЕНИЙ ПОКАЗАТЕЛЕЙ Т-СИСТЕМЫ ИММУНИТЕТА У БОЛЬНЫХ С РАЗНОЙ КОНТРОЛИРУЕМОСТЬЮ БРОНХИАЛЬНОЙ АСТМЫ И ИХ ПРОГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ

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Резюме. *Цель*: выяснение прогностического значения изменений Т-системы иммунитета на основании изучения их особенностей у больных бронхиальной астмой (БА) с различной ее контролируемостью. *Материалы и методы.* Обследовано 133 больных БА: 11 пациентов с контролируемой, 63 пациента с частично контролируемой и 59 пациентов с не контролируемой БА. Группу контроля составили 36 волонтеров. Определяли содержание лейкоцитов, относительное и абсолютное количество лимфоцитов, пан-Т-клеток, Т-хелперов, цитотоксических Т-лимфоцитов, иммунорегуляторный индекс (ИРИ), пролиферативный ответ Т-клеток на фитогемагглютинин (ФГА) в реакции бласттрансформации (РБТЛ), а также характер и частоту изменений этих показателей. *Результаты*. При контролируемой БА выявлено уменьшение количества пан-Т-клеток и Т-хелперов, увеличение числа цитотоксических Т-лимфоцитов, что в 44,4 % случаев обусловило уменьшение ИРИ. У большинства больных с частичным контролем БА определялось референтное и повышенное содержание Т-хелперов, уменьшение количества цитотоксических Т-клеток и ИРИ, что является характерными признаками срыва адаптационных иммунологических механизмов. При неконтролируемой БА определялось повышение числа Т-клеток, уменьшение количества цитотоксических Т-лимфоцитов и рост ИРИ, что свидетельствовало об иммунологической дезадаптации. Угнетение пролиферативного ответа Т-клеток на ФГА было зафиксировано только у 24,6 % пациентов, что может быть косвенным признаком стероидной резистентности. *Выводы*. Индивидуальные изменения показателей Т-системы иммунитета могут использоваться для прогнозирования контролируемого или неконтролируемого течения БА. Эти подходы позволяют заранее пересмотреть схему лечения больных и предупредить потерю контроля над болезнью.
Ключевые слова: бронхиальная астма, Т-система иммунитета, контролируемость.

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Uncontrolled bronchial asthma (BA) remains at the center of attention of pulmonologists, allergists and immunologists from many countries of the world [8, 4, 14, 15, 28]. It is due to a significant decrease in the quality of life of patients with this disease, frequent occurrence of life-threatening conditions and significant material damage. Thus, according to a new European study by J. Frederick, 94 % of patients with severe BA had uncontrolled course of the disease [24]. By results of an online survey of patients from the UK, Germany, France, Spain and Portugal European researchers also found a high level of uncontrolled course of severe asthma. In this case, 74 % of patients reported asthma attacks, 32 % of patients – about three or more asthma exacerbations during the last three months. Every fifth respondent reported an aggravation that lasted more than a week and affected their personal and professional life. Patients with uncontrolled asthma noted a more significant decline in their quality of life (HRQoL – Health-related quality of life), more severe disability and more significant financial costs than patients with controlled asthma [24] according to L. K. Lee et al. [26]. The indirect costs of patients with uncontrolled asthma were twice as high as in patients with good disease control, and direct and total costs were 1.5 times higher.

Under current conditions, timely diagnosis and prognosis of uncontrolled asthma becomes of particular importance: the appearance of anti-asthma drugs – "target" or "biological" drugs — increases the potential for asthma therapy and the desired control of the disease. These drugs include humanized monoclonal antibodies against immunoglobulin E (omalizumab), anti–interleukin (tralokinumab, mepolizumab, reslizumab, dupilumab, benralizumab, tezepelumab), anti–leukotriene (zileuton, pobilucast, montelukast, pranlukast, verlukast, etc.) [11, 14, 16, 19, 20]. Typically, these drugs are prescribed to patients with uncontrolled asthma and ineffectiveness of standard therapy.

Given the heterogeneity of mechanisms of development of uncontrolled asthma, their elucidation continues to be one of the priority directions of diagnosis and prognosis [15, 23]. It is known that the basis of the pathogenesis of asthma is immunological mechanisms: they are responsible for the initiation, development and persistence of allergic inflammation in the respiratory tract, and their diversity and expressiveness form different variants of the course of the disease – its phenotype, severity, control, frequency of exacerbations, etc. Therefore, the study of immunological disorders in asthma still continues despite the large volume of already obtained data.

It has been shown that in the immune response, both in relatively healthy people and in patients with asthma, an important role belongs to T-lymphocytes because they are able to attract and activate other cells of inflammation with the help of cytokines. When evaluating the state of the immune system, the determination of the content of helper and cytotoxic T-cells (respectively, $CD4^+CD8^-$ and $CD4^-CD8^+$ lymphocytes), as well as their ratio – the immunoregulatory index (IRI), is of particular importance. Normally effector factors (cytotoxic cells and antibodies) in organism should be produced as much as they are necessary for elimination of one or another antigen. Insufficient content and activity of cytotoxic T-lymphocytes leads to the prevalence of T-helper cells, which increases the immune response and is manifested by stimulation of antibody production and/or prolonged activation of T-effectors. In turn, the excess content and activity of cytotoxic T-lymphocytes, on the contrary, can lead to a rapid suppression of the immune response and even induction of immunological tolerance (a state when the immunological response to a certain antigen does not develop at all). An increase in the content and activity of cytotoxic lymphocytes is at the basis of the pathogenesis of autoimmune processes and the development of delayed-type hypersensitivity [9].

A lot of research is devoted to the study of changes in T-cell immunity parameters in BA. But presented by different authors, the data is quite controversial. So, when studying the balance of subpopulations of T-lymphocytes in patients with varying severity of BA, A. S. Abdulamir et al. [17] did not reveal significant changes in T-helper and cytotoxic T lymphocyte and IRI levels. In the work of E. Y. Barabash, et all. [1], there were no differences between subpopulations of CD-lymphocytes in healthy persons and patients with asthma. At the same time, according to S.Y. Lee et al., [27] there was a marked increase in IRI in patients with asthma in comparison with the reference values of this indicator.

In the study of Y. V. Skibo et al. changes in the content of cytotoxic cells in mild atopic asthma were not detected, whereas during its severe course the authors determined an increase in the number of T-helper cells and a decrease in the content of cytotoxic T-lymphocytes [9]. Similar results were obtained by us in children with different severity of asthma [3] and adult patients with asthma [13].

To detect the immunological markers of the uncontrolled course of atopic BA, M. V. Smolnikova et al. [10] studied cell immune parameters in children with controlled and uncontrolled atopic asthma, and the content of pan-T cells ($CD3^+$ lymphocytes), T–helper cells ($CD4^+$ lymphocytes) and cytotoxic T cells ($CD8^+$ lymphocytes) was found to be lower than in the group of children with controlled course of this disease. As markers of the uncontrolled course of atopic asthma in children, these authors suggest to use low blood levels of T lymphocytes and cells with the phenotype $CD4^+$ and $CD8^+$. In the study of L. Y. Litvinets et al. [5] in children with uncontrolled and partially controlled asthma a decrease in IRI was demonstrated, based on a decrease in the percentage of $CD4^+$ lymphocytes and an increase in the percentage of $CD8^+$ lymphocytes. Such a contradiction in the data obtained in various studies may be due to errors in the formation of groups, methodological differences, the lack of an individualized approach to the analysis of the results of immunological examination of patients and other factors.

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The aim. This work was carried out at the expense of the state budget of Ukraine and aimed at founding out the predictive value of changes in T-cell immune parameters based on the study of their peculiarities in patients with BA with different controllability. To achieve this goal it was supposed to solve the following tasks:

1. In the groups of patients with controlled, partially controlled and uncontrolled BA the content of leukocytes, relative and absolute content of lymphocytes, pan-T cells, T-helper/inducers, cytotoxic T-lymphocytes and immunoregulatory index were determined.

2. In patients with controlled, partially controlled and uncontrolled BA the functional activity of T-cells for their proliferative response to the mitogen was determined.

3. In patients with controlled, partially controlled and uncontrolled BA the frequency and nature of changes in T-immune parameters were determined.

Materials and methods. The study was conducted on the basis of pulmonology department SO «National Institute of Phthysiology and Pulmonology named after F. G. Yanovsky NAMS of Ukraine» (NIFPNAMNU) and in the laboratory of clinical immunology of the same institution.

The work is based on the analysis of data (including archival) of a complex clinical and immunological examination of 133 patients with asthma that underwent inpatient and ambulatory treatment in the department of bronchoobstructive pulmonary diseases in patients with tuberculosis NIFPNAMNU, had no serious concomitant infectious diseases and informed consent to participate in these studies. The control group consisted of 36 volunteers without clinical signs of somatic and infectious pathology (blood donors) aged 19 to 57 years, including 23 men and 13 women.

Distribution of patients with asthma with different controllability by gender and age is presented in table 1. Analysis of these data showed that the overwhelming majority of the surveyed were women with uncontrolled asthma (74.6 %). In the other two groups female patients also dominated that matches the gender specificities of the disease. The average age of patients with asthma was (49.2 ± 1.2) years, including (45.2 ± 5.0) years in the group of patients with controlled asthma, (47.6 ± 1.7) years in the group of patients with partial control of the disease (47.6 ± 1.7) and (51.4 ± 1.9) years in a group of patients with uncontrolled asthma ($p > 0.05$). It should be noted that more than 90.0 % of patients were of working age, and there was no statistically significant difference between the proportions of patients of different age groups in controlled, partially controlled and uncontrolled asthma, which indicates the homogeneity of the studied groups on this basis. In the group of patients with controlled asthma, 54.5 % had a mild course of the disease, 44.5 % had BA of moderate severity, and none of these patients had severe asthma. In patients with partially controlled asthma, mild course of BA was detected only in 15.9 % of patients, most patients (74.6 %) had BA of moderate severity, and one of 10 patients in this group (9.5 %) had severe asthma. In patients with uncontrolled course of BA, mild asthma was detected in 10.2 %, moderate – in 44.1 % of patients and severe BA – 45.8 %.

To assess the control of asthma, we used criteria based on international guidelines (GINA, 2014) [21] and presented in the unified clinical protocol for primary, secondary (specialized) medical care "Bronchial asthma" [6].

In standard immunoassay, the phenotyping of lymphocytes (Lf) was performed by means of two-color flow laser cytometry (flow cytofluorometer FACSCalibur, Canada) using monoclonal antibodies (MABs) to differentiate antigens (BECKMAN COULTER, USA) and determine the relative and absolute content of pan-T cells ($CD3^+19^-$ Lf), T-helper / inducer ($CD4^+8^-$ Lf) and cytotoxic T cells ($CD4^-8^+$ Lf) [7]. To detect the imbalance of immunoregulatory subpopulations of T cells, we determined the immunoregulatory index (IRI) – the ratio of contents of $CD4^+8$ Lf and $CD4^-8^+$ Lf. To calculate the absolute content in the blood of particular lymphocyte populations, we used the leukogram parameters determined on the hematological analyzer ABX-miscros 60 (France). The proliferative response of Lf to phytohemagglutinin (PHA) was studied in the lymphocyte blast transformation reaction (LBTR) [2, 12].

The digital material obtained in the course of the research in each individual sample was checked for normal distribution of quantities. To check the normality of the data distribution, S.N. Lapach's technique technique was used [4] – NORMSAMP-1 function that is embedded in the Excel environment. The obtained results determined the choice of the method of further statistical data processing to confirm the reliability of the results.

Paired Student's T-test (for dependent and independent samples) was used to assess the reliability of the differences in the mean values of the indices in the nor-

Table 1. Distribution of patients with bronchial asthma with different controllability by gender and age

Control of the course of asthma:	Gender				Age							Total	
	male		female		up to 30 years old		31-50 years old		51-70 years old		older than 70 years old		
	n	%	n	%	n	%	n	%	n	%	n	%	n
Controlled	4	36.4	7	63.6	3	27.2	4	36.4	4	36.4	0	0.0	11
Partially controlled	20	31.7	43	68.3	10	15.9	24	38.1	28	44.4	1	1.6	63
Uncontrolled	15	25.4	44	74.6	5	8.5	21	35.6	28	47.5	5	8.5	59
Total	38	29.2	92	70.8	16	12.3	48	36.9	60	46.2	6	4.6	133

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mal distribution. The difference between the scores was considered statistically verified by the p-value (p) between the groups that was equal to or less than 0.05. In the absence of the normality of distribution, to confirm the validity of the difference between the indicators, the Wilcokson criterion two-sample test was used. In the analysis of individual changes of the studied indicators, the method of alternative variation was used [4].

Retaining the results of the research and their mathematical processing were carried out with the help of licensed software products included in the Microsoft Office Professional 2007 package, the license Russian Academic OPEN No Level 43437596.

Results and discussion. Analysis of the data presented in table 2, demonstrated a statistically confirmed increase in the relative and absolute content of lymphocytes in the group of patients with controlled asthma — (46.0 ± 4.1) % and (3.48 ± 0.6) × 10^9 / l at a reference value of (34.0 ± 1.7) % and (2.34 ± 0.16) × 10^9/l, respectively ($p < 0.05$). In this group, an adaptive decrease in the relative content of pan-T cells ($CD3^+19^-$ Lf) was observed up to (36.6 ± 4.1) % at the reference values of (67.2 ± 1.2) % ($p < 0.05$), absolute content of T-helper ($CD4^+8^-$ Lf) — up to (0.69 ± 0.06) × 10^9 / l at the reference values of (0.89 ± 0.06)× 10^9 / l, ($p < 0.05$), as well as an increase in the relative content of cytotoxic T-lymphocytes ($CD4^-8^+$ Lf) to (33.8 ± 0.06) %, with reference values (26.4 ± 0.6) %, ($p < 0.05$). There was no statistically verified difference between the absolute content of these cells and the immunoregulatory index, as well as the proliferative response of T cells to the PHA compared to the reference parameters (table 3).

In the group of patients with partially controlled asthma there was an increase in the content of leukocytes in the blood up to (9.0 – 0.5) × 10^9 / l; the reference value is (6.8 ± 0.4) × 10^9 / l, ($p < 0.05$). This was due to the increased content of lymphocytes ((41.1 ± 1.5) %, $p < 0.05$ and (3.71–0.28) × 10^9 / l, $p < 0.05$), however the relative and absolute numbers of the latter did not differ from those in the group of patients with controlled asthma (see table 2). Reduced relative and absolute content of pan-T cells ($CD3^+19^-$ Lf), which were recorded in a group of patients with partially controlled asthma ((37.4 ± 1.6) % and (1.3±0.10) × 10^9 / l, respectively, $p < 0.05$), also did not differ from these indicators in the group of patients with controlled disease (see table 3). Attention is drawn to the fact that in the group of patients with partial control of asthma, the relative number of T-helpers ($CD4^-8^+$ Lf) was significantly lower both in comparison with the reference value and in comparison with this indicator of the group of

Table 2. The content of leukocytes and lymphocytes in patients with bronchial asthma with different controllability

Contents	Reference Indexes	Patients with BA:											
		controlled (n = 9)				partially controlled (n = 63)				uncontrolled (n = 59)			
		M	m	Me	Min–Max	M	m	Me	Min–Max	M	m	Me	Min–Max
white blood cells 10^9/l	6.8 ± 0.4	7.3	1.0	6.8	3.2-11.2	9.0*	0.5	8.5	4.0-25.7	7.9	0.4	7.2	3.5-18.2
lymphocytes %	34.8 ± 1.7	46.0*	4.1	46.0	24.0-59.0	41.1*	1.5	40.0	21.0-65.0	38.2	2.2	36.3	6.0-79.0
10^9/l	2.34 ± 0.16	3.48*	0.6	3.30	1.01 -6.02	3.71*	0.28	3.22	1.36-13.62	3.02*#°	0.22	2.79	0.26-8.26

Notes: * – the difference between the indicator and the reference is statistically verified ($p < 0.05$); # – the difference between the indicator and the group of patients with controlled asthma is statistically confirmed ($p < 0.05$); ° – the difference between the indicator and the group of patients with partially controlled asthma is statistically confirmed ($p < 0.05$).

Table 3. Indicators of T-system of immunity in patients with asthma with different control of the disease

Indices	Reference Indexes	Patients with BA:											
		controlled (n = 9)				partially controlled (n = 57)				uncontrolled (n = 64)			
		M	m	Me	Min — Max	M	m	Me	Min — Max	M	m	Me	Min — Max
T-cell content ($CD3^+19^-$ Lf)													
%	67.2 ± 1.2	36.6*	4.1	39.0	20.0-52.0	37.4*	1.6	36.0	15.,0-70.4	52.9*#°	2.1	51.0	20.0-82.7
10^9/l	1.69 ± 0.1	1.28	0.30	1.08	0.38-2.75	1.35*	0.10	1.13	0.43-3.81	1.50#	0.11	1.37	0.09-4.54
Content of T-helper ($CD3^+19^-$ Lf)													
%	38.6 ± 1.2	36.6	0.4	37.0	34.0-38.5	24.5*#	1.9	22.0	7.0-57.8	41.8°	1.7	41.1	29.3-62.5
10^9/l	0.89 ± 0.06	0.69*	0.06	0.67	0.65-0.72	0.95#	0.11	0.83	0.18-3.11	0.90#	0.14	0.69	0.14-3.53
Content of cytotoxic T cells ($CD4^-8^+$ Lf)													
%	26.4 ± 1.3	33.8*	0.6	35.6	33.2-36.5	17.2#	1.2	17.0	8.0-36.0	24.6#°	1.7	24.8	11.9-40.5
10^9/l	0.60 ± 0.03	0.64	0.04	0.64	0.59-0.68	0.66	0.07	0.57	0.16-2.04	0.52°	0.06	0.52	0.06-0.96
Immunoregulatory index													
u.o.	1.5 ± 0.1	1.1	0.2	1.1	0.9-1.3	1.5	0.1	1.3	0.7-2.9	1.9#°	0.2	1.7	0.7-3.7
Proliferative response of T-lymphocytes to PGA													
%	57.7 ± 1.7	58.7	5.4	60.0	23.3-78.0	58.2	1.8	61.2	21.3-83.0	61.0	1.2	62.0	38.7-81.0

Notes: * — the difference between the indicator and the reference is statistically verified ($p < 0.05$); # — the difference between the indicator and the group of patients with controlled asthma is statistically confirmed ($p < 0.05$); ° — the difference between the indicator and the group of patients with partially controlled asthma is statistically confirmed ($p < 0.05$).

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patients with controlled asthma. At the same time, the absolute content of these cells, on the contrary, was significantly increased compared to the indicator of the group of patients with controlled disease (respectively, $(0.95 \pm 0.11) \times 10^9$ / l and $(0.69–0.06) \times 10^9$ / l, $p < 0.05$), which is characteristic of the disruption of the adaptation mechanisms. Low relative content of cytotoxic T-cells in the group of patients with partial asthma control ((17.2 ± 1.2) %, $p < 0.05$) was not accompanied by an adequate decrease in the absolute amount of this subpopulation of lymphocytes. The increase in the immunoregulatory index compared with this indicator in the group of patients with controlled asthma did not find statistical confirmation (1.5 ± 0.1) and (1.1 ± 0.2), $p > 0.05$), but this trend was quite clear. There were no differences in the T cell proliferative response to the PGA (see table 3).

In the group of patients with uncontrolled asthma, as in groups with controlled and partially controlled asthma, there was also an increase in the absolute number of lymphocytes (corresponding to $(3.02–0.22) \times 10^9$ / l, $p < 0.05$), but it was significantly less clear (see table 2). The decrease in the relative content of pan-T cells ($CD3^+19^-$ Lf) was also significantly less pronounced than in the groups of patients with controlled and partially controlled asthma((52.9 ± 2.1) %, (36.6 ± 4.1) %, (37.4 ± 1.6) %, respectively, $p < 0.05$). No changes in the absolute content of pan-T cells ($CD3^+19^-$ Lf) were observed: these indices did not differ from the reference ones. In the group of patients with uncontrolled asthma, changes in the relative and absolute number of T helper were not observed (see table 3), but a statistically confirmed decrease in the absolute content of cytotoxic T-lymphocytes was observed (up to $(0.52–0.06) \times 10^9$ / l as compared with $(0.64 – 0.04) \times 10^9$ / l and $(0.66 – 0.07) \times 10^9$ / l,$p < 0.05$, respectively). This led to an increase in the immunoregulatory index, which was significantly higher than in the groups with controlled and partially controlled asthma: respectively, (1.9–0.2) compared with (1.1 ± 0.2), $p < 0.05$ and (1.5 ± 0.2), $p < 0.05$, respectively. The revealed changes indicated a further failure of the adaptive immunological mechanisms in patients with asthma with a lack of its control. The proliferative response of T-cells to the PGA, as in patients from the other two groups, did not differ from the reference

Analysis of individual changes in the content of leukocytes and lymphocytes in the blood of patients with asthma with different control of the disease did not reveal any validated differences between the groups: in the majority (from 55.6 % to 75.9 % of

Table 4. The direction and frequency of changes in the parameters of T-immunity system in patients with asthma with different disease control

Groups of surveyed	n	Direction and frequency of changes in immunological parameters					
		Reduced		Reference		Increased	
		n[1]	% (M ± m)	n[1]	% (M ± m)	n[1]	% (M ± m)
BA	The content of leukocytes (10^9/l)						
controlled by	9	1	11.1 ± 10.5	5	55.6 ± 16.6	3	33.3 ± 15.7
partially controlled	63	0	0.0	47	74.6 ± 5.5	16	25.4 ± 5.5
uncontrolled	58	3	5.2 ± 2.9	44	75.9 ± 5.6	11	19.0 ± 5.2
BA	The content of lymphocytes (10^9/l)						
controlled by	9	1	11.1 ± 10.5	5	55.6 ± 16.6	3	33.3 ± 15.7
partially controlled	63	0	0.0	43	68.3 ± 5.9	20	31.7 ± 5.9
uncontrolled	58	3	5.2 ± 2.9	40	69.0 ± 6.1	15	25.9 ± 5.8
BA	T-cell content ($CD3^+19^-$ Lf) 10^9/l						
controlled by	9	4	44.4 ± 16.6	3	33.3 ± 15.7	2	22.2 ± 13.9
partially controlled	57	21	36.8 ± 6.4	25	43.9 ± 6.6	12	21.1 ± 5.4
uncontrolled	58	20	34.5 ± 6.2	22	37.9 ± 6.4	16	27.6 ± 5.9
BA:	Content of T-helper cells ($CD4^+8^-$ Lf) 10^9/l						
controlled by	9	0	0,0	9	100,0	9	0
partially controlled	31	4	12.9 ± 6.0	21	66.7 ± 8.5#	6	20.4 ± 7.2#
uncontrolled	24	1	4.2 ± 4.1	19	79.2 ± 8.3	4	16.6 ± 7.6
BA:	Content of cytotoxic T cells ($CD4^-8^+$ Lf) 10^9/l						
controlled by	9	0	0.0	8	89.8 ± 10.5	1	11.1 ± 10.5
partially controlled	31	9	29.0 ± 8.1#	15	48.4 ± 9.0#	7	22.6 ± 7.5
uncontrolled	24	11	45.8 ± 10.2#	11	45.8 ± 10.2#	2	8.3 ± 5.6
BA	Immunoregulatory index (u.o.)						
controlled by	9	4	4.4 ± 16.6	4	44.4 ± 16.6	1	11.1 ± 10.5
partially controlled	31	17	54.8 ± 8.9	10	32.3 ± 8.4	4	12.9 ± 6.0
uncontrolled	24	9	37.5 ± 9.9	9	37,5 ± 9.9	6	25.0 ± 8.8
BA	Proliferative response of T-lymphocytes to PGA (%)						
controlled by	9	3	33.3 ± 15.7	5	55.6 ± 16.6	1	11.1 ± 10.5
partially controlled	58	24	41.4 ± 6.5	24	41.4 ± 6.5	10	17.2 ± 5.0
uncontrolled	57	14	24.6 ± 5.7°	36	63.2 ± 6.4°	7	12.3 ± 4.4

Notes: # — the difference between the indicator and the group of patients with controlled asthma is statistically confirmed ($p < 0.05$); ° — the difference between the indicator and the group of patients with partially controlled asthma is statistically confirmed ($p < 0.05$).

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cases), these indices did not differ from the reference ones, their increase took place at each third and fifth patient, and the decrease was recorded only in isolated cases (table 4).

In the analysis of the directions and frequency of changes in T-cell immune parameters (see table 4), it was found that in controlled BA, the adaptive reduction in the absolute content of pan-T cells occurred in 44.4 % of cases, and their high content was found in 22.2 % of patients. There was no change in the absolute number of T-helper cells ($CD4^+8^-$ lymphocytes) in any patient in this group, and only in one case there was an increase in the content of cytotoxic T-cells ($CD4^-8^+$ Lf). However, 44.4 % of patients in this group determined a decrease in immunoregulatory index, indicating an imbalance of T-helper cells and cytotoxic T-cells in favor of the latter.

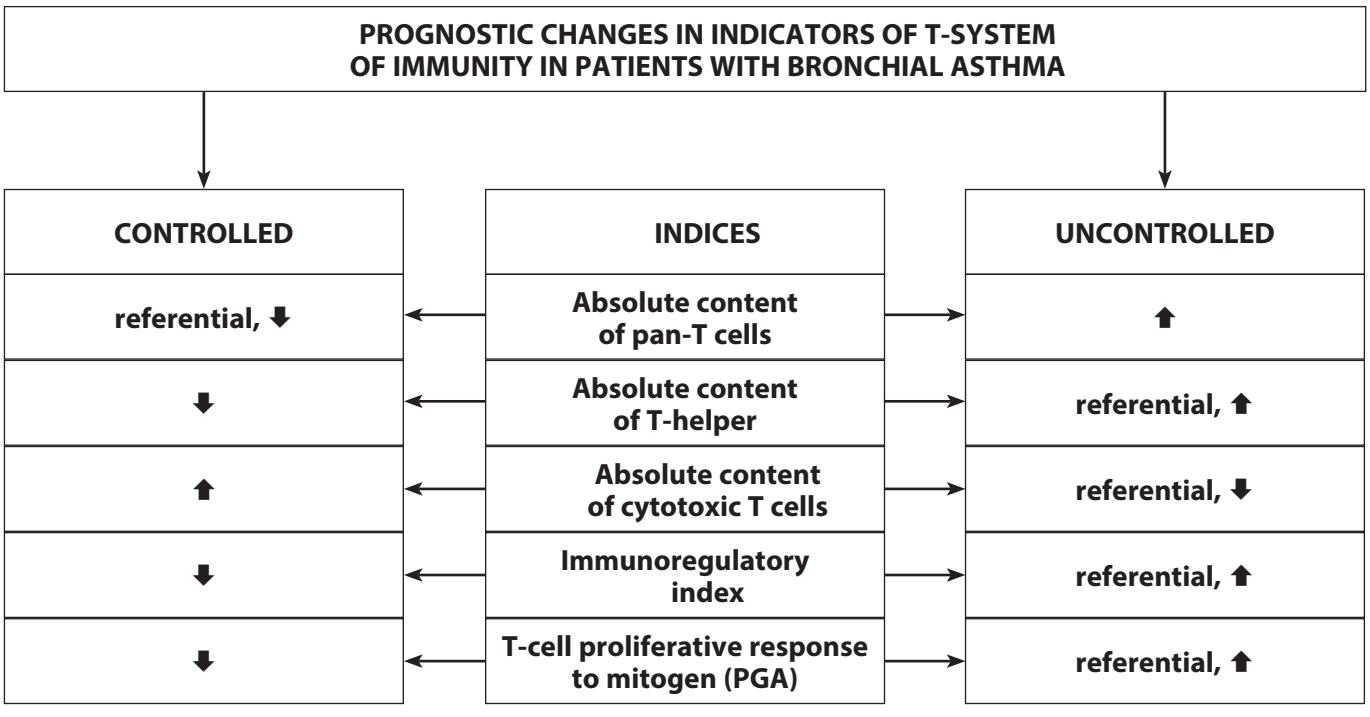
In the group of patients with partially controlled asthma, there was no significant difference in the frequency of changes in the content of pan-T cells compared with the group of patients with controlled asthma, at each fifth the T-helper population increased and in 29.0 % of patients in this group there was a decrease in the absolute amount of cytotoxic T-lymphocytes, indicating the depletion of adaptation mechanisms in these patients (see table 4).

Adaptive reduction of IRI was registered in 54.8 % of patients with partial control of asthma, and in the remaining 45.2 % of cases this indicator was indicative (32.3 %) and high (12.9 %) patients, which is a characteristic manifestation of immunological maladaptation in BA.

In the group of patients with uncontrolled asthma, there was no difference in the frequency and direction of change in the absolute number of pan-T cells compared to the groups of patients with asthma with a controlled and partially controlled course of this disease. The decrease in T-helper content was noted only in one case (4.2 %) and in 45.8 % there was a decrease in the absolute amount of cytotoxic T-lymphocytes. The decrease in IRI was established only in 37.5 % of patients with uncontrolled asthma, 37.5 % of the deviation was not within the reference range, and the increase of this indicator was established in 25.0 % of patients in this group.

The suppression of the proliferative response of T cells to the PGA was detected in 33.3 % of patients with controlled asthma, in 41.4 % of patients with partial control of the disease, and only in 24.6 % of patients with uncontrolled asthma, and in the remaining patients of these groups (66.7 %, 58.6 % and 75.4 % respectively), the proliferative response of T cells to the PGA was either referential or even elevated. Given the powerful anti-inflammatory therapy that is used in patients with asthma with poor disease control, such a low incidence rate of T-cell proliferative response to PGA may be an indirect indication of decreased lymphocyte susceptibility to glucocorticosteroids (GCS) – steroid resistance, and can be considered an indication for appropriate examination.

Thus, in the group of patients with controlled asthma, minimal changes occurred in leucograms, which were manifested by an increase in the absolute content of lymphocytes. In this group, there was a decrease in the relative content of pan-T cells (which was recorded



Conditional signs: ⬆ — increase, gain; ⬇ — reduction, inhibition

Picture 1. Changes in T-immune system indexes in patients with bronchial asthma and their prognostic value.

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in 44.4 % of cases), mainly due to the T-helper subpopulation and an increase in the relative content of cytotoxic T-lymphocytes, which did not lead to an increase in the absolute content of these cells, however caused an adaptive reduction of the immunoregulatory index in patients in this group.

In the group of patients with partially controlled asthma changes in leukograms were more pronounced than in controlled cases. They were characterized by leukocytosis and lymphocytosis. The reference and increased absolute content of T-helper cells ($CD4^{-}8^{+}$ Lf), which was recorded in the vast majority of patients, a decrease in the absolute content of cytotoxic T-cells and an increase in IRI are signs of failure of adaptive immunological mechanisms.

In the group of patients with uncontrolled asthma, changes in leukograms were associated with an increase in the absolute content of lymphocytes in each third patient. A characteristic feature of the state of the T-cell immunity was a statistically confirmed decrease in the absolute content of cytotoxic T-lymphocytes (45.8 %), which led to an increase in the immunoregulatory index and indicated a further failure of the adaptive immunological mechanisms. Inhibition of the proliferative response of T-lymphocytes to the mitogen in this group was observed only in 24.6 % of patients, which, given the strong therapy of patients, may be an indirect indication of a decrease in the sensitivity of lymphocytes to GCS in 2/3 of patients with uncontrolled asthma.

Conclusion. Thus, individualized changes in the parameters of the T-cell immunity (according to the data of the general immunogram) can be used to predict the controlled or uncontrolled course of bronchial asthma in patients with this disease (Fig. 1):

1. In determining the reduced or reference absolute content of pan-T cells, reduced absolute content of T-helper cells, increased absolute amount of cytotoxic T-lymphocytes, reduction of immunoregulatory index and inhibition of T-cell proliferative response to phytohaemagglutinin, it is possible to predict disease control and a good response to therapy with glucocorticosteroids.

2. In determining the elevated absolute pan-T cell content, the reference or elevated absolute T-helper content, the reference or reduced absolute number of cytotoxic T-lymphocytes, the elevated immunoregulatory index, and the reference or elevated T-cell proliferative response to phytohaemagglutinin, one can predict uncontrolled bronchial asthma and probable resistance to glucocorticosteroids, which may cause inadequate efficiency in their use.

These approaches allow you to preview the treatment regimen of these patients and prevent their loss of control over the disease.

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