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Clinical and pathogenetic features of optimization of diagnostics and treatment of inflammatory cardiomyopathy diseases

Características clínicas y patogenéticas de optimización de diagnósticos y tratamiento de enfermedades inflamatorias de cardiomiopatía

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Abstract

This article presents data on the development of pathogenetic relationships expressing TLR 2, 4 initiations of inflammation in the mucosa of the colon and, as a consequence, the appearance of the main clinical symptoms of the disease. As well as the data obtained can serve as a theoretical justification for the search and conduct additional methods of pharmacological correction of the revealed violations. The results of the study allow to expand the diagnostic algorithm, to optimize the tactics of management of patients with IBD, to predict early recurrence of the disease.

Keywords: Inflammatory cardiomyopathy disease, cellular and humoral immunity, TLR receptor, Pro-inflammatory interferon

Resumen

Este artículo presenta datos sobre el desarrollo de relaciones patogénicas que expresan el inicio de la inflamación de TLR 2, 4 en la mucosa del colon y, como consecuencia, la aparición de los principales síntomas clínicos de la enfermedad. Además, los datos obtenidos pueden servir como una justificación teórica para la búsqueda y llevar a cabo métodos adicionales de corrección farmacológica de las violaciones reveladas. Los resultados del estudio permiten ampliar el algoritmo de diagnóstico, optimizar las tácticas de manejo de los pacientes con EII, para predecir la recurrencia temprana de la enfermedad.

Palabras clave: Enfermedad de miocardiopatía inflamatoria, inmunidad celular y humoral, receptor TLR, interferón proinflamatorio

Introduction

Inflammatory cardiomyopathy disease has been studied only in part, leading to a lack of clear diagnostic criteria and treatment standards for ulcerative colitis (UC) and Crohn's disease (CD) (L. Peyrin-Biroulet et al., 2007). There is a general consensus among leading experts on IBD that CD and UC are the results of the combined effects of global environmental change, different genetic variations, qualitative and quantitative changes in the composition of intestinal microflora, and disorders of the innate and adaptive immune response (Y.A. Ogura, et al.,2001; Schmidt C. et al., 2005). In this case, none of these circumstances can independently cause and (or) support the inflammatory process in the intestine. It is possible that this explains the variety of clinical manifestations of diseases and patient response to therapy. Given the direct contact of the intestinal mucosa with the microflora and the absence of damaging reactions to this interaction in healthy individuals, there is an opinion about the presence of special protective mechanisms, violations in which cause clinical manifestation of GCS (Korzenik, J.R., 2005; Rakoff-Nahum S., 2004). At the same time, increased permeability of the intestinal mucosa due to genetic factors and direct contact with bacteria and their waste products can play a leading role in the formation of chronic inflammation (Hugot, J.P.,2003). Currently, an important role in the etiopathogenesis of IBD is assigned to the factors of innate and adaptive immunity. In recent years, there has been clear progress in the study of the role of toll-like receptors(TLR) in the provision of innate and adaptive immunity, which has defined a new view on the nature of immune processes in the body (Allison, A. C., 2005).

TLR was found to recognize highly conservative structures of pathogenic microorganisms, the so-called patterns associated with microorganisms (Allison, A.C., 2005). A

number of defects in the TLR system: ligand recognition disorders, TLR expression, signal transduction, can lead to the development of severe diseases (H. Ito, 2005; Cario E. 2010).

It was found that in IBD accompanied by massive cell destruction, a large number of endogenous ligands are released, and this leads to the activation of intracellular signaling pathways TLR (R. Caprilli., 2009). In turn, excessive activation of TLR and the production of uncontrolled amounts of proinflammatory cytokines can determine the development of systemic inflammatory response, further tissue damage, the formation of complications of the underlying disease (Yamamoto-Furusho J. K., 2007). The study of the TLR system is important in understanding the pathogenesis of diseases associated with tissue damage. To date, there have been a number of studies of the role of TLR in the development of IBD, which are not numerous, and their results are rather contradictory (E. Cario, 2000; Frolova L.,2008).

Activation of TLR entails an enhanced synthesis of antimicrobial peptides (AMPS) that provide nonspecific protection against pathogens on the mucous surface[1,7]. Namely AMP forms the composition of the commensal microflora and contribute to the maintenance of intestinal homeostasis. One of the representatives of endogenous AMP is lactoferrin (LF) – a non-heme iron-binding glycoprotein related to transferrins, positioned as a highly sensitive marker in IBD and colon tumor diseases, acting as an indicator of the activity of the process, the effectiveness of treatment[2,5]. Research on the involvement of LF in maintaining gut microbalance is limited to the study of fecal LF only[8,26]. It is well known that the intestinal mucosa has a special place in the formation of General and local immunity, a key component of which is secretory IgA (SIgA)[3,8,25].

Comprehensive analysis of Toll-like receptors in ulcerative colitis and Crohn's disease.
Innate immunity affects the timely activation of adaptive and largely determines its nature. Along with genetic factors, intestinal microflora provokes the emergence of IBD[9]. Innate protective mechanisms for combating pathogens. The rate of reaction depends on the occurrence of the pathogen-associated molecular patterns, which are a set of bacteria and viruses (lipopolysaccharides, peptidoglycan, flagellin, lipoproteins). With the discovery of Toll-receptors understanding of the mechanism of congenital protection cleared. According to one version[10] they play an important role in the pathogenesis of the disease. Timely recognition of pathogen-associated molecular patterns stimulates the launch of adaptive immunity[27].

The discovery of Toll-receptors is associated with the name of the German scientist Christiane Nusslein-Volhard. The gene he identified in 1985 in flies-Drosophila, was responsible not only for polarization in embryonic development but also for the antifungal effect. The Association of microorganisms with pagon by (pathogen-associated molecular patterns (hereinafter: RAMR) was proposed in the theory of C. Janeway "On the recognition of images". Later, a similar receptor was found on the monocytes of the individual. It was called the Toll-receptor. Modern science has discovered 11 Toll-receptors in humans. Mice have one more. Such receptors are found in all mammalian cells that come into direct contact with pathogens[11,32,33].

According to their structure, Toll-receptors are transmembrane proteins, which include 3 main parts: the zone of responsibility for ligand binding, TIR-domain and the site of protein attachment to the cell membrane[12] [P. 70]. The main function of Toll-receptor reduced to the discernment of a pathogenic agent, alarm about the danger and conduct response measures for the prevention of contamination microflora. Thus, this receptor is responsible for the balanced work of innate and acquired immunity. Each receptor is characterized by its own ligand, which triggers the body's response to an alien agent. For example TLR 2 corresponds to lipoproteins and peptidoglycan gram-positive bacteria, TLR 4 lipopolysaccharide of gram-negative bacteria, and TLR 6 — shimotani yeast[13,18]. Consequently, a violation in the work of Toll-receptors both upward and downward can be the cause of various diseases. The weakening of function testifies to immunodeficiency, and strengthening — to presence of inflammatory disease and the unhealthy reaction of an organism to the cells and tissues[14,15,28].

Interest in Toll-receptor increases, especially in the field of hematological pathology. In the cancer process, he takes a dual role. On the one hand, it is a participant of anti-tumor measures, on the other hand — helps pathogenic tumor cells to evade immune reaction[16,17]. The receptor promotes the development of a renal disease, which develops into renal failure. In terms of the development of inflammatory cardiomyopathy diseases there is no consensus on the role of Toll-receptors[29].

Protection of the mucous surface from pathogens is possible due to the intensive synthesis of antimicrobial peptides when TLR is activated. Antimicrobial peptides play a dual role in the activation of immune function[20]. On the one hand, their synthesis is accelerated by the introduction of an alien agent or damage to the epithelial surface. On the other hand, their number also increases with inflammation. Obviously, it is antimicrobial peptides that play a major role in maintaining intestinal homeostasis and provide control of intestinal microflora. These protein molecules are an integral part of innate immunity. In the body, they play the role of endogenous antibiotics, as they destroy the structure and function of the cytoplasmic membrane of microorganisms, which destroys them[30,31].

Lactoferrin is one of the representatives of antimicrobial peptides. It is a polyfunctional protein from the transferrin family. Its distinctive feature is high sensitivity to inflammatory cardiomyopathy diseases and colon cancer[21]. Protein performs the following functions: bactericidal, antiviral, immunomodulatory, disinfecting and transport. Ecogeneration causes a change of Pro-inflammatory in-

terferon- (IFN-), IL-1, IL-6 and victoria secret of the tumor and reduces the production of IL-5 and IL-10. It is likely that this result is achieved due to the ability of a positively charged N-terminal domain of the LF molecule to bind oligosaccharide[21].

During the contact of lactoferrin with the CD 14 is the synthesis of molecules that direct the white blood cells in the inflammatory areas of the cardiomyopathy, and activation of immune cells. Also, this multifunctional protein suppresses transcription factors. It binds free iron from damaged cells and removes toxic radicals. This manifests its anti-inflammatory function. Lactoferrin can act as an indicator of the presence of IBD since the inflammatory process increases its concentration in the blood and other biological fluids. In a number of studies[1,22] the relationship between the level of this protein and inflammatory activity in patients with Crohn's disease and ulcerative colitis was emphasized. Fecal lactoferrin can be regarded as an indicator of the effectiveness of treatment.

The gastrointestinal mucosa is a natural barrier to pathogenic bacteria, so it needs increased protection. The protective function is manifested by the well-functioning of the innate and acquired immune systems. Lactoferrin, mucus, lysozyme, and cytokines act as instruments of innate immunity. The acquired immunity is represented by antibodies. One of them is secretory immunoglobulin A (hereinafter: SIgA), which forms strong compounds with pathogenic microorganisms, thereby preventing their further spread[23].

SIgA is often referred to as a marker of local immunity. It is produced by activated B cells in the mucous membrane, and its Assembly is carried out on the walls of important body systems, so for doctors, it is of interest to the level in biological fluids. It acts as an indicator of secretory immunity in pathology and characterizes the effectiveness of therapy. The antibody and can be detected in the serum. The pathology is evidenced by its increase in serum, which is due to active synthesis in damaged cells[24].

Low levels of immunoglobulin are also a negative factor. It may indicate the presence of food allergy, celiac disease, predisposition to autoimmune diseases. It is worth noting that modern science has a meager supply of research on the analysis of the behavior of immunoglobulin A in various biological substrates. Thus, the causes of the Genesis of IBD are not only genetic and external factors but also the nature of the interaction of innate immunity with foreign agents and the adequacy of the response of the adaptive immune response. It follows that it is necessary to consider the elements of innate and adaptive immunity against the background of modification of the intestinal microsphere in the ligament.

Materials and methods

The study included the actual material of an open prospective cohort study in parallel groups of 40 patients with Ulcerative colitis and Crohn's Disease (table. 1).

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Table 1. Distr3ibution of patients with inflammatory cardio-myopathy diseases				
Diagnosis	Ulcerative colitis (US)	Crohn disease (CD)		
research group	I n=19	II n=21		
subgroups	Ia	Iб	IIa	IIб
	6 (33,3%)	13 (66,7%)	8 (38,1%)	13 (61,9%)
Total	36 (100%)	21 (100%)		

After a comprehensive examination of patients and verification of the diagnosis of IBD, in accordance with the inclusion and exclusion criteria, two research cohorts were formed: I cohort - 19 patients with relapse of UC (12 - women and 7 - men), aged 23-70 years (mean age 39.0±1.4 years) and II research cohort - 21 patients with relapse of CD (14 - women and 7 - men), mean age 42.6±3.2 years. Patients I cohort depending on the location of the inflammatory process were ranked into 2 groups: Ia - 6 (33.3%) patients with distal UC, and IB - 13 (66.7%) patients with a total form of the disease. Patients in study cohort II were divided into 2 subgroups depending on segmental localization of intestinal lesion: IIA subgroup - 8 (38.1%) patients with colonic localization, IIB subgroup - 13 (61.9%) patients with combined lesions of the colon and small intestine. The control group consisted of 30 healthy volunteers (20 women, 10 men), average age - 27.4±5.7 years.

After isolation of the study groups, all patients underwent a special laboratory examination, including immunological blood tests with the determination of CD4+, CD8+, CD16+ HCT test, CEC, Ig G, M, A, TLR expression determination 2, 4 on the surface of blood monocytes of patients.

At the second stage of the study, the patients were re-ranked into groups depending on the activity and severity of the relapse of the disease, on the variant of the prescribed 8-week course therapy, during which the standards of medical care for patients with Inflammatory cardiomyopathy disease (IBD) and the experience of previous drug therapy were used.

At the end of the clinical study, clinical and endoscopic remission reached 7 patients with UC (5 women and 2 men), and 3 patients with CD (2 women, 1 man), which amounted to 25 % of patients included in the study. Clinical and endoscopic remission was understood as the ab-

sence or very insignificant severity of the main clinical symptoms and complete healing of the mucous membrane.

Clinical, endoscopic, morphological and special (immunological) research methods were used to implement scientific tasks. The results of a comprehensive study were included in the individual patient registration card (IRK).

The endoscopic study was conducted using a floor-by-floor segmental examination of the colon and terminal small intestine using the standard technique of video ileo colonoscopy using the EXERA II Olympus video system and CF-180H video colonoscopes both in the normal mode and in the narrow spectrum illumination mode (NBI). In the course of diagnostic video ileo colonoscopy, a semi-quantitative score assessment of inflammatory erosive and ulcerative changes in the small and large intestine was carried out, based on macroscopic changes in CO, supplementing the activity indices of IBD (Mayo D. Rachmilewitz, CDAI).

Morphological study of ileo-colonization allowed to dynamically assess the degree of activity of inflammatory changes in the small and large intestines in the process of the course of drug therapy, to exclude dysplastic changes. Special immunological laboratory examination included determination of TLR 2, 4 expressions on blood monocytes as well as extended immunological examination of blood with determination of CD4+, CD8+, CD16+, HCT test, CEC, Ig G, M, A. TLR Expression on peripheral blood monocytes was determined by immunofluorescence test.

Results and Discussion

During the examination, cellular and humoral immunity, indicators of neutrophilic link of the immune system (nst SP., Nst art., To art.). The state of cellular immunity was assessed by determining the number of subpopulations of T-lymphocytes (CD4+, CD8+), NK-cells (CD16+). The number of cells expressing the membrane marker (CD16+) and cells having helper-inductive properties (CD4+) remained unchanged in comparison with the control group (p>0.05). Humoral indicators presented in the study by lymphocytes with CD19+ on their surface increased by 1.2 times, which was 37% higher than the control group (p<0.05). In patients with relapse of UC, the level of IgG and IgA exceeded the values of the group of healthy volunteers by 1.3 and 1.1 times, respectively, while the content of IDM did not differ. The number of CIC in the serum of patients with relapse of UC reached 81.1±2.4.e. that was 1.3 times higher than the level of the control group values (p<0.05). A study of the microbicidal activity of neutrophils showed a statistically significant 1.4-fold decrease in stimulated neutrophil activity and a similar decrease in the stimulation coefficient compared to the control group (p<0.05).

Thus, the analysis of the parameters of the immune status in patients with relapse of UC indicates the activation of the cell link of the immune system, violation of the processes of intercellular cooperation, manifested in the imbalance of the ratio of subpopulations of T-lymphocytes in the direction of increasing the number of cells with cytotoxic activity, increased activity of the humoral link of the immune system, accompanied by an increase in the concentration of Ig A and G, as well as depletion of neutrophil-phagocytic link of the immune system. During remission, the normalization of cellular immune status parameters and a slight activation of the humoral component of the immune system, as well as a moderate depletion of phagocytic reserves were observed.

The state of Toll-receptors 2, 4 in patients with ulcerative colitis.In our study, TLR 2, 4 expression was evaluated in patients with different phases of UC (table. 2).

Table 2. Expression of TLR 2, 4 on monocytes in patients with ulcerative colitis during relapse and remission of the disease

Ulcerative Colitis Phase	Relapse n=19	Remission n=21	Control group n=30
CD4+, %	79,1±0,3*, ***	61,0±0,3**	68,1±0,3
CD8+, %	12,6±0,5*, ***	5,3±0,4	2,9±0,9
CD16+, %	10,2±0,8*, ***	5,1±0,7	3,1±0,8

Note: * - p<0,05 in comparison with control group, ** - p < 0.05 in comparison with control group, *** - p<0,05 in comparison with indicators in the period of remission.

The mean values of CD4+ cells during relapse of UC were 79.1±0.3%, which exceeded 1.2 times the values during remission (p<0.05). The expression level of CD4+ was 1.5 times higher than in the remission phase and was 3 times higher in comparison with the control group. The increase in CD4+ was 10.2±0.8%, which was 2.4 and 3.1 times higher, respectively than in the period of remission of UC and in the group of healthy volunteers (p<0.05).

As a result of the analysis of the distribution of TLR expression in patients in the period of recurrence of ulcerative colitis, depending on the prevalence of the inflammatory process in the colon, it was revealed that the distal shape of the YAK, the expression of TLR increased by 7.7% (p>0.05), while left form 16.3%, and in the form of total YAK the increase reached a maximum value - 85,2±1,2 18.5% exceeded the level in the control group (p<0.05). No statistically significant changes in the number of monocytes expressing TLR 2 were revealed during the intragroup analysis. The dynamics of TLR 4 expression on the surface of monocytes was more significant. Thus, the number of CD14+CD284+ cells was increased 2.4 times (p<0.05) in comparison with the control group in the case of distal colon lesions. In the group with left-sided localization of the inflammatory process, expression increased 3 times, in the total form of UC the studied index increased 3.7 times (p<0.05). The dynamics of the increase in the number of monocytes expressing TLR 6 also depended on the localization of the inflammatory process: in the distal

form there was a twofold increase in indicators, in the left-sided and total form of UC the increase was 9.8±0.4 and 10.7±0.3, which was 2.9 and 3.1 times higher than the values of the group of healthy volunteers (p<0.05) (table. 3).

Table 3. Expression of TLR 2, 4 on monocytes depending on the extent of the inflammatory process during acute ulcerative colitis

Localization of the inflammatory process	Ia n=6	Ib n=13	Control group n=30
CD4+,%	71,9±1,8	82,4±0,2*	64,5±0,2
CD8+,%	9,4±0,1*	10,8±0,9*	2,8±0,7
CD16+,%	8,3±0,7*	7,5±0,5*	3,1±0,5

Note: *- p<0.05 compared to the control group

When comparing the expression of TLR 2, 4 in the period of remission of UC with the indicators of the control group, the results were similar, but no statistical differences were found. Analysis of the revealed changes in TLR 2, 4 expression indicates a decrease in the activity of the innate immune response system in patients with UC (table. 4). When comparing the results presented in tables 3 and 4, it was found that the differences in the expression of CD4+ in patients with a left-sided and total form of UC significantly differ from the studied values during remission (p<0.05). The difference in expression increases with an increase in the prevalence of inflammation: in the left-sided and total forms of 14.1% and 14.8%, respectively, exceeding the baseline by 1.1 times, while in the distal form of UC differences in the expression of CD4+ were only 5.2% (p>0.05). Analysis of the dynamics of the increase in the relative number of monocytes expressing TLR 4 revealed statistically significant differences in the period of relapse and remission of UC in all groups of patients: in the distal form, the expression of CD8+ increased 1.3 times. in left-sided and total forms – 2.1 times (p<0.05). The dynamics of increase in CD4+ indicators in different phases of the disease showed statistically significant differences in the distal, left-sided and total forms: 1.4, 2.2 and 2.6 times, respectively (p<0.05).

Table 4. Expression of TLR 2, 4 on monocytes depending on the extent of the inflammatory process in patients with ulcerative colitis in remission

Study group	Ia n=8	Iб n=13	Control group n=30
CD4+	62,5±4,1**	63,2±0,9**	64,7±0,2
CD8+	5,1±0,4**	5,2±0,1**	2,9±0,5
CD16+	5,2±0,8**	4,9±0,5**	3,1±0,6

Note: ** - p>0.05 compared to the control group

Table 5. Expression of TLR 2, 4 on monocytes in patients with ulcerative colitis depending on the severity of the disease

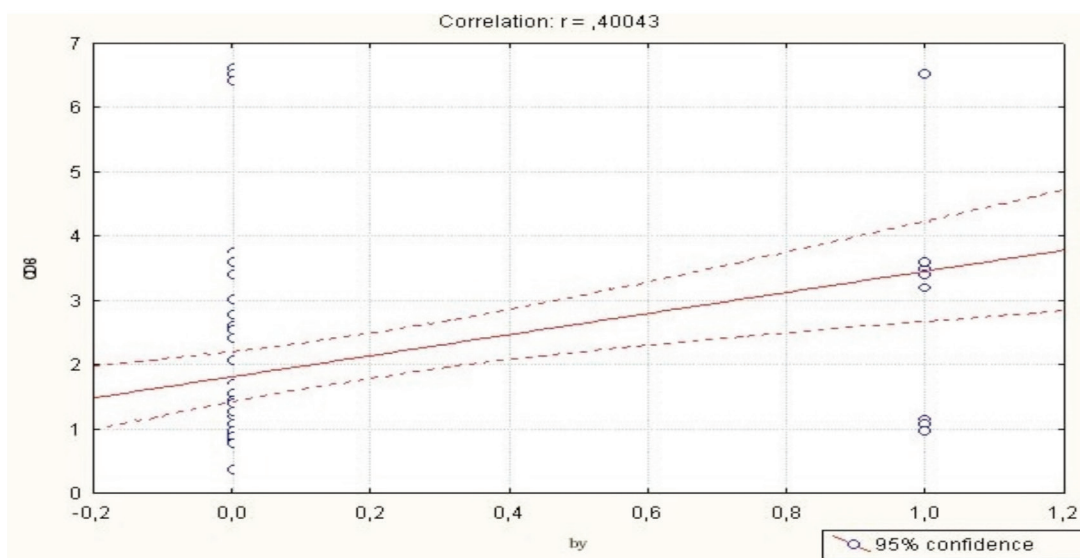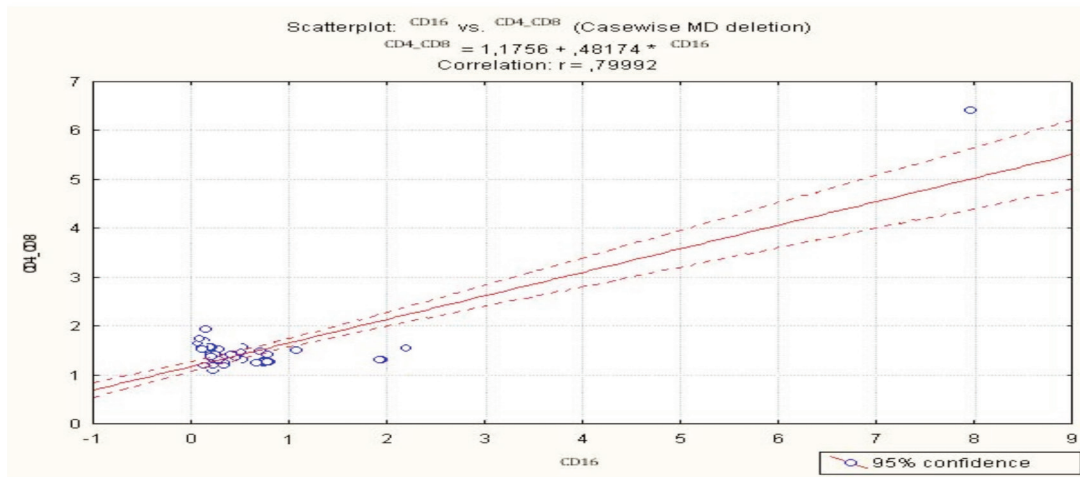| Degree of severity	easy n= 4	average n= 9	heavy n= 6	Control group n= 30
CD 4+	77,0±0,8	80,2±0,6*	84,1±0,4*	62,4±0,3
CD8+	9,1±0,3*	12,4±0,2*	13,4±0,1*	3,9±0,8
CD16+	8,9±0,1*	9,1±0,3*	11,2±0,6*	3,1±0,1

Note: *- p>0.05 compared to the control group

The results of the intragroup analysis of TLR 2, 4 expressions on monocytes depending on the severity of the disease are presented in table 5. In the mild course of UC revealed a slight difference of 8.1% (p>0.05) between the expression of CD4+ during exacerbation and the control group. In severe cases, the increase in the studied index was 1.1 times (p<0.05). Expression of CD8+ was increased by 2.1 and 3.2 times with mild severity and moderate course; in severe course of the disease the difference was 13.4±0.1, which was 3.2 times higher than the control group (p<0.05). The mild course of UC was accompanied by an increase in the number of CD16 + cells by 2.4 times, the average severity by 2.6 times, and the severe course by 3.2 times, respectively (p<0.05) (table. 5).

When conducting the correlation analysis revealed the presence of a direct high correlation between the expression of CD4+, CD8+, CD16+ on the surface of monocytes and the severity of the YAK (r=0,59, of 0.72, r=0.48, respectively, p<0.05). Thus, the presence of the actual relationship between the degree of activity of the inflammatory process in the colon, severe course of UC and the increase in monocytes with the phenotype CD4 +, CD8+, CD16 + allows to make a reasonable conclusion about the increase in the production of components of innate immunity in relapse of common forms of UC.

The next stage of the study was to determine the relationship between the expression of CD4 +, CD8+, CD16 + and clinical symptoms of UC. Correlation analysis showed a moderate positive relationship between the number of monocytes expressing CD4+, CD8+, CD16 + and the frequency of acts of defecation per day in patients with UC during relapse (r=0,41, r=0,44, r=0,39, respectively, at p<0,05), stool consistency (r=0,58, r=0,52, r=0,79, respectively, at p<0,05), the presence of pathological impurities in feces (r=0,44, r=0,79, r=0,62 accordingly, at p<0.05).

The results of the evaluation of changes in expression of CD4 +, CD8+, CD16 + depending on the severity of disorders of colonic normality of patients with relapse of UC are presented in table 6. Positive correlations between the number of CD4+ cells and the content of enterococci in feces of patients with UC (r=0.57, p<0.05), staphylococci (r=0.40, p<0.05), Clostridium (r=0.63, p<0.05), respectively, were revealed.

The results of the study showed that the increase in the number of monocytes expressing CD8+ was significantly correlated with the increase in titers of Proteus and Klebsiella in coprofiltrates (r=0.52 and r=0.46, p<0.05).

Scatterplot: CD16 vs. CD4_CD8 (Casewise MD deletion)
CD4_CD8 = 1,1756 + ,48174 * CD16
Correlation: r = ,79992

Correlation: r = ,40043

Conclusions

The obtained results allow to present a possible variant of pathogenetic relationships development as follows: an increase in opportunistic microorganisms in the lumen of the colon stimulates increased activity of innate immunity factors in the form of an increase in the number of monocytes expressing TLR 2, 4, further initiation or enhancement of the inflammatory process in the mucosa of the colon, and, as a consequence, the appearance of the main clinical symptoms of the disease. As well as the data obtained can serve as a theoretical justification for the search and conduct additional methods of pharmacological correction of the revealed violations. The results of the study allow to expand the diagnostic algorithm, to optimize the tactics of management of patients with IBD, to predict early recurrence of the disease.

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