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THE RELATIONSHIP BETWEEN IMMUNE INFLAMMATION MARKERS AND RHEOLOICAL INDICATORS DYNAMICS AFTER TREATMENT OPTIMIZATION IN PATIENTS WITH POST-INFARCTION ANGINA

PANAKHOVA NURENGIZ A., *senior assistant of the Department of clinical pharmacology of Azerbaijan Medical University, Azerbaijan, AZ 1007, Baku, Gasymzade str., 14, e-mail: mic_amu@mail.ru*

Abstract. ***The aim of the study*** was to determine dynamics and correlation between immune inflammation markers and rheological indicators before and after optimized treatment in patients with post-infarction angina. ***Material and methods.*** 47 patients [41 (87,2%) men and 6 (12,8%) women with average age of 59,9±1,1] who experienced coronary events within 3-6 months (subacute stage) after myocardial infarction have been examined. 25 practically healthy individuals formed the control group. Rheological indicators (fibrinogen, thrombin time, INR values) and immune inflammation markers (TNF-alpha, IL-8, CRP) were investigated in the indicated patients group. ***Results and discussions.*** According to the results of the research, destabilization of disease in patients with post-infarction angina in subacute stage was characterized by hyperactivity of cytokine system (TNF-alpha, IL-6, IL-8) and statistically reliable growth of severe phase mediators (C-reactive protein, fibrinogen) in comparison with practically healthy people and patients with chronic ischemic heart disease (CIHD). Significant correlations between TNF-alpha and IL-6 (r=0,912; p<0,01), CRP and IL-8 (r=0,466; p<0,01), TNF-alpha and fibrinogen (r=0,566; p<0,01), IL-8 and CRP (r=0,466; p<0,01), IL-6 and fibrinogen (r=0,605; p<0,01) were found in the group with post infarction angina (n=47). ***Conclusion.*** Immunomodulators and selective anti-inflammatory drugs are appropriate as a part of treatment and pharmacotherapeutic optimization of post-infarction angina with hypercytokinemia.

Key words: Post-infarction angina pectoris, immune inflammation, cytokines, severe phase mediators.
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КОРРЕЛЯЦИОННАЯ ВЗАИМОСВЯЗЬ МАРКЕРОВ ИММУННОГО ВОСПАЛЕНИЯ И ДИНАМИКИ РЕОЛОГИЧЕСКИХ ПОКАЗАТЕЛЕЙ ПОСЛЕ ОПТИМИЗАЦИИ ЛЕЧЕНИЯ ПАЦИЕНТОВ С ПОСТИНФАРКТНОЙ СТЕНОКАРДИЕЙ

ПАНАХОВА НУРЕНГИЗ АЛАДДИН гызы*, старший лаборант кафедры клинической фармакологии Азербайджанского медицинского университета, Азербайджан, AZ 1007, Баку, ул. Гасымзаде, 14, e-mail: mic_amu@mail.ru*

Реферат. ***Цель*** – определение динамики и корреляционной взаимосвязи маркеров иммунного воспаления и реологических показателей до и после оптимизированного лечения пациентов с постинфарктной стенокардией. ***Материал и методы.*** В исследование было включено 47 пациентов с коронарными явлениями в течение 3–6 мес (подострая стадия) после инфаркта миокарда. Контрольную группу составили 25 практически здоровых лиц. Средний возраст у 41 (87,2%) мужчины и 6 (12,8%) женщин составил (59,9±1,1) года. Реологические показатели (фибриноген, время тромбина, значения МНО) и маркеры иммунного воспаления (TNF-альфа IL-6, IL-8, CRP) были изучены в указанной группе пациентов. ***Результаты и их обсуждение.*** Согласно результатам исследования дестабилизация заболевания у пациентов с постинфарктной стенокардией (подострая стадия) характеризовалась повышенной активностью цитокиновой системы (TNF-альфа, IL-6, IL-8) и статистически достоверным ростом медиаторов тяжелой фазы (С-реактивный белок, фибриноген) по сравнению с практически здоровыми людьми и больными хронической ишемической болезнью сердца (ИБС). Значительная корреляция между TNF-альфа и IL-6 (r=0,912; p<0,01), CRP и IL-8 (r=0,466; p<0,01), TNF-альфа и фибриногеном (r=0,566; p<0,01), IL-8 и CRP (r=0,466; p<0,01), IL-6 и фибриногеном (r=0,605; p<0,01) были обнаружены в группе пациентов с постинфарктной стенокардией (n=47). ***Выводы.*** Иммуномодуляторы и селективные противовоспалительные

препараты целесообразно включать в лечение постинфарктной стенокардии с гиперцитокинемией для оптимизации фармакотерапии.
Ключевые слова: постинфарктная стенокардия, иммунное воспаление, цитокины, медиаторы тяжелой фазы.
Для ссылки: Панахова, Н.А. Корреляционная взаимосвязь маркеров иммунного воспаления и динамики реологических показателей после оптимизации лечения пациентов с постинфарктной стенокардией / Н.А. Панахова // Вестник современной клинической медицины. – 2020. – Т. 13, вып. 1. – С.36–41. ***DOI:*** 10.20969/VSKM.2020.13(1).36-41.

Introduction. It was shown the important role of inflammation in both beginning and progressing of atherosclerosis, as well as in transferring stable atherosclerosis plaque to unstable stage [1]. Elevated inflammatory markers has bad prognostic importance in patients with non-stable angina pectoris in comparison with stable angina [2, 3].

An important role in the formation of the pathogenesis of cardiovascular diseases play an imbalance of pro- and anti-inflammatory cytokines, such as interleukins: interleukin-1 beta (IL1), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-α) [4, 5, 6, 7, 8]. Inflammatory cytokines (TNF-α, IL-1, IL-6) are the markers of acute coronary events risk [9].

IL-6 not only increases the plasma concentration of C-reactive protein (CRP), but also the level of fibrinogen, an inhibitor of plasminogen activator-1 (PAI – plasminogen activator inhibitor-1), an inhibitor of plasminogen activator-2 (PA1-2) and serum amyloid A protein. An increase in TNF-α is associated with repeated coronary events in patients with coronary heart disease (CHD) [10]. High concentrations of TNF-a in the blood of CHD patients are associated with a poor prognosis [11]. Elevated IL-6 values are independent predictors of increase of 12-month mortality incidence [12].

Aim. To determine dynamics and correlation relationship of immune inflammation markers and rheological indicators before and after optimized treatment in patients with post-infarction angina

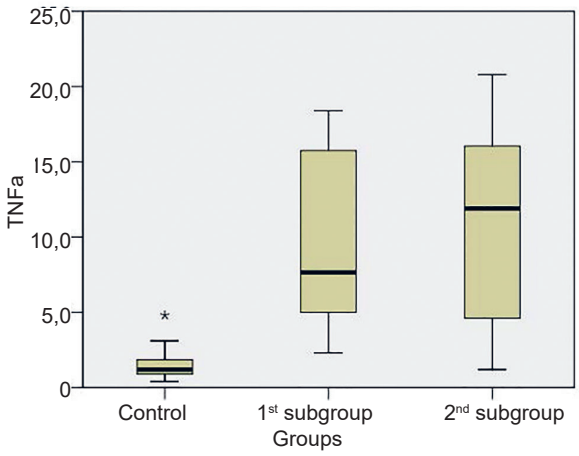
Material and methods. 47 patients having re-angina within 3–6 months (half-severe stage) after myocardial infarction have been included to the research. Control group is composed of 15 practically healthy persons. Average age of 41 (87,2%) men, 6 (12,8%) women was 59,9±1,1. Ischemic heart disease (IHD) was diagnosed on the basis of clinical instrumental information (typical pain syndrome in a quite state, specification of ECG changes during daily monitoring, veloergometry test, echocardiography). As well as depression of ST segment has been in ECG and/or the number of attacks has increased with passing changes as inversion of T-wave in two or more than attacks before creation of new Q-wave in ECG. The patients have been divided into two subgroups. First subgroup (*n*=20) has been treated only traditionally with aspirin or clopidogrel (100%), b-adrenoblockers (92%), nitrates (75%), ACE-inhibitors (57%), dihydropyridine Ca-blockers (8%) according to the severity degree of the disease. Second subgroup was additionally taken immune-modulator and selective anti-inflammatory drugs (**s**elverin 100 mg in injection and meloksikam 15 mg daily) during 2 months.

Statistical analysis was performed using the software Microsoft Excel 7,0 and STATISTICA 6.0. The results obtained were expressed as M±m. Confidence of values' differences was determined by Student's and sign criteria. Difference was considered confident with $p<0,05$. For determination of correlations between indicators we calculated correlation coefficients by Pirson ad built correlation structures.

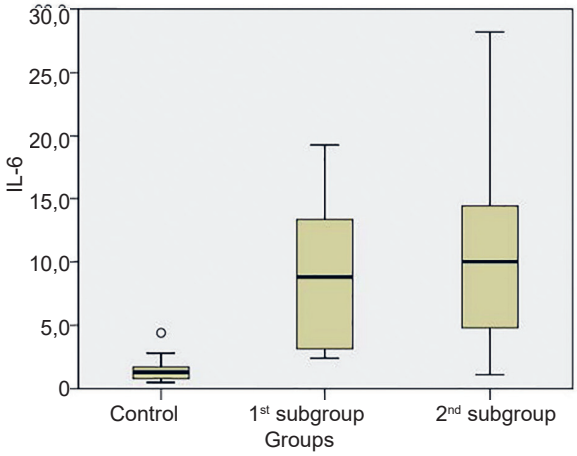
Results and discussion. Results of trial were showed at the following *pictures 1, 2*.

As show in the diagrams, immune-inflammation markers (TNF-alpha, IL-6, IL-8) and average concentration of fibrinogen were statistically significantly increased in patients comparing to healthy individuals ($p<0,01$) *(table 1)*.

As shown in the table 1 there is no statistic difference between two subgroups in inflammatory markers before treatment. TNF-alpha was 11,2±2,0 before therapy, and 7,5±1,4 ($p=0,051$) after treatment in 1st subgroup; 13,3±2,2 before and 6,3±0,3 ($p<0,001$) after therapy in



Picture 1. TNF-alpha indices in patients in 1st and 2nd subgroups



Picture 2. The IL-6 level in patients of 1st and 2nd subgroups and control group

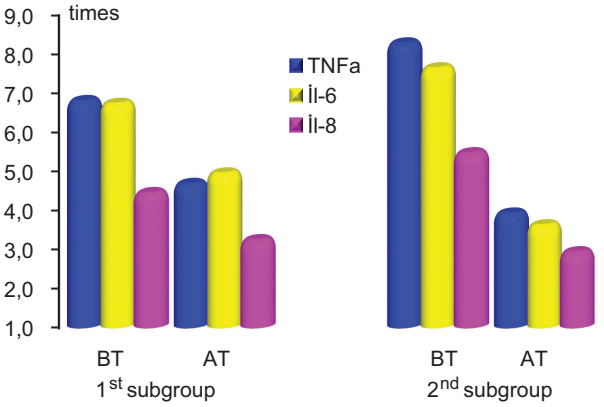
Table 1

Dynamics of cytokines plasma content before and after treatment in patients groups

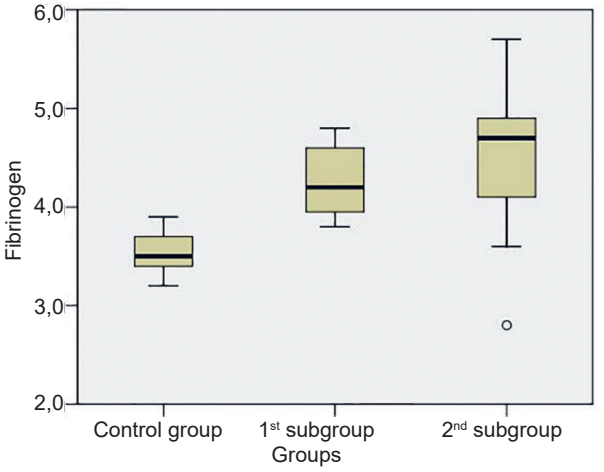
Indices	1st group *(n=20)*		2nd group *(n=27)*		Control group *(n=25)*
	Before treatment	After treatment	Before treatment	After treatment	
TNF-alpha, *pg/ml*	11±2,0***	7,5±1,4***	13,3±2,2***	6,3±1,18**^^	1,6±0,3
IL-6, *pg/ml*	10,0±1,9***	7,4±1,5**	11,3±0,8***	5,4±0,8**^^	1,5±0,3
IL-8, *pg/ml*	4,8±0,8***	3,5±0,6**	5,9±0,9***	3,1±0,4**^^	1,1±0,3
CRP, *mg/l*	14,7±1,9**	9,5±0,9*^	14,2±0,6***	8,4±0,7*^^^	6,7±0,5

Comparing 1st subgroup to control group *p<0,05, **p<0,01, ***p<0,001.
Comparing 2nd subgroup to control group #p<0,05, ##p<0,01, ###p<0,001.
Comparing before and after treatment in the same group ^p<0,05, ^^p<0,01, ^^^p<0,001.

2nd subgroup. IL-6 was 10,0±1,9 before, and 7,4±1,5 (p=0,104) after therapy in 1st subgroup; 11,3±1,8 before, and 5,4±0,8 (p<0,001) in 2nd subgroup. IL-8 was 4,8±1,8 before the treatment, then 7,1±1,2 (p=0,122) in 1st subgroup; 10,4±0,8 before, and 3,5±0,6 (p<0,001) after treatment in 2nd subgroup. CRP was 14,7±1,9 before treatment, 9,5±0,9 (p<0,05) after therapy in 1st subgroup; 14,2±0,6 was before, 8,4±0,7 (p<0,001) after therapy in 2nd subgroup. Fibrinogen was 4,29±0,08 before the treatment, then 3,97±0,06 (p<0,01) in 1st subgroup; and 4,56±0,13 before, and 3,77±0,066 (p<0,001) after treatment in 2nd subgroup *(pictures 3, 4)*.



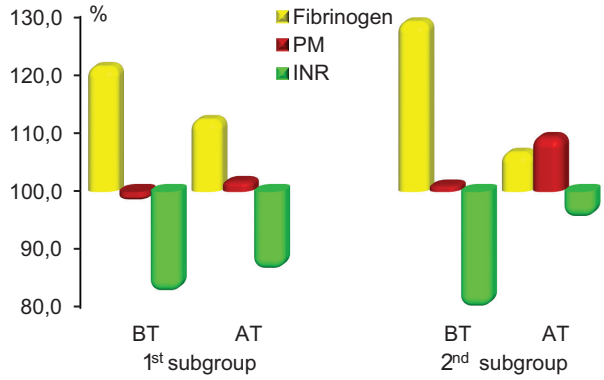
Picture 3. Dynamics of cytokines before and after the treatment in the examined patients groups.
Note: 100 is conventionally accepted as control. BT – before treatment; AT – after treatment



Picture 4. Comparison of fibrinogen level in patients in 1st and 2nd subgroups with control group

The level of fibrinogen before therapy was higher in the 1st and 2nd subgroups compared with the control group: 4,29±0,08; 4,56±0,13 and 3,53±0,06, respectively (p<0,001 for both cases).

After 2 months therapy, the fibrinogen level was 3,97±0,06 in the 1st subgroup (the differences were statistically significant compared to the pretreatment level; p<0,01); in the 2nd subgroup 3,77±0,06 (the differences in comparison with the pre-treatment level was also statistically significant (p<0,001). Both indices compared with the control group differed significantly (p<0,001 and p<0,05) *(picture 5)*.



Picture 5. Dynamics of rheological indicators in the examined patients.
Note: 100 is conventionally accepted as control. BT – before treatment; AT – after treatment

There was no statistically significant difference in INR between the 1st and 2nd subgroups. In patients with post infarction angina, this indicator before the start of therapy was 1,18±0,02 (their variations within the group were 1,09–1,48) and 1,14±0,02 (variations within the group were 1,0–1,36).

These indicators in both groups compared with the control group differed significantly p<0,001 (for both cases). In the control group, it was 1,43±0,06 (with fluctuations within the group 1,1–2,1). The obtained results indicate that in the majority of patients with post infarction angina pectoris (95%), although the INR was within the normal range, compared to the control it was 1,2 times lower (p<0,001). After treatment, the levels of INR in the 1st and 2nd subgroups were 1,24±0,02 and 1,37±0,03, respectively, increasing insignificantly compared with baseline values before treatment *(table 2)*.

Table 2

Correlation between clinical laboratory indicators of patients and rheological indicators and immune-inflammation markers in patients post-infarction angina pectoris (a, b)

a						
Cytokines	Age	Severity degree of disease	High blood pressure	EF	CRP	Fibrinogen
TNF-a	0,381**	0,357*	0,043	-0,399**	0,276	0,566**
IL-6	0,334*	0,322	0,247	-0,246	0,261	0,605**
IL_8	0,230	0,398**	0,165	-0,396**	0,466**	0,563**
CRP	0,000	0,291*	-0,010	0,361*	------	0,378**
Fibrinogen	0,154	0,365	0,245	-0,246	0,378**	-------
INR	0,60	-0,250	-0,330	0,082	-0,232	-0,552**

b							
Cytokines	INR	TNF-a	IL-6	IL-8	Cholesterol	HDL	LDL-
TNF-a	-0,242	----	0,912**	0,884**	0,267	-0,013	0,221
IL-6	-0,248	-,912**	----	0,906**	0,130	0,071	-0,221
IL-8	-0,220	0,884**	0,906**	----	0,376**	-0,134	0,367
CRP	-0,232	0,261	0,261	0,466**	0,626**	-0,315	0,778**
Fibrinogen	-0,552	0,566**	0,605**	0,563**	0,211	0,024	-0,330

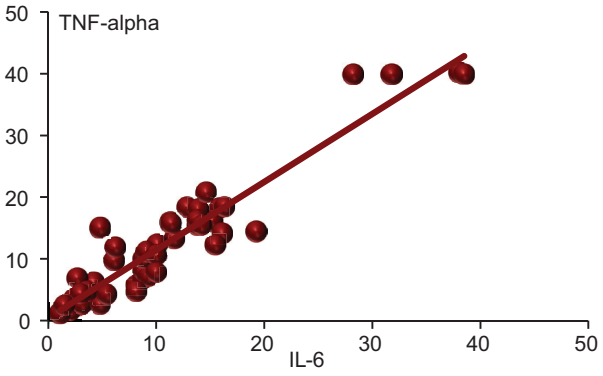
Note: significant correlation coefficient *p<0,05; **p<0,01.

During analyzing the results of the research it is shown that there is strong dependence between the levels of inflammation markers in both group, as well as the severity degree of the disease and rheological indicators *(picture 6)*.

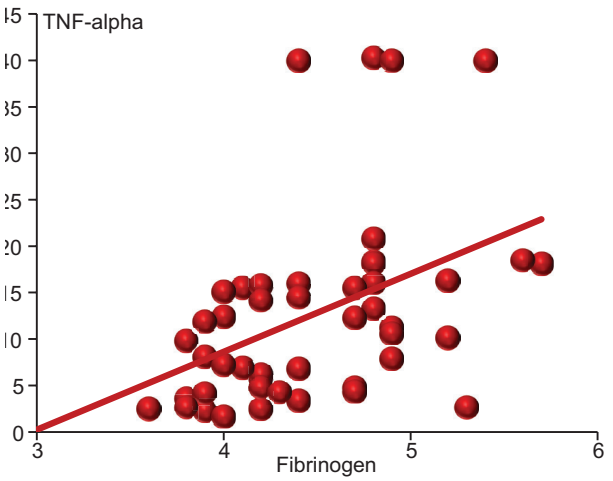
Strong correlation between TNF-alpha and IL-6 level in the patients with post-infarct angina was determined (r=0,912; p<0,01) *(picture 7)*.

Correlation between TNF-alpha and fibrinogen levels in patients with post-infarct angina pectoris (r=0,566; p<0,01) *(picture 8)*.

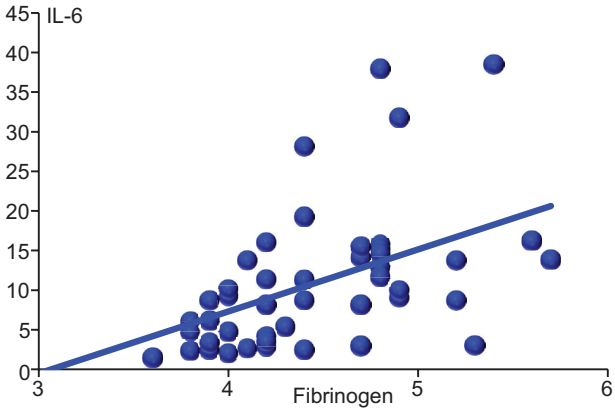
It was defined that hypersecretion of IL-6 and TNF-alpha can provokes recurrence of myocardial infarction, burden of the clinical course and prognosis of the disease. In the light of the data obtained, destabilization of the course of IHD after myocardial infarction is characterized by hypersecretion of pro-inflammatory cytokines, increased levels of C-reactive protein and hyperactivity of immune inflammatory reactions.



Picture 6. Correlation between TNF-alpha and IL-6 in patients with post-infarct angina before treatment (n=47)



Picture 7. Correlation between TNF-alpha and fibrinogen in patients with post-infarct angina before the treatment (n=47)



Picture 8. Correlation relationship between IL-6 and fibrinogen (n=47).
Close correlation between the level of IL-6 and fibrinogen (r=0605; p<0,01)

There is lack of investigations studied the relationship of immune inflammatory reactions with hemodynamics during different variants of the clinical course of IHD [7, 8]. So the role of immune inflammatory reactions in the destabilization and more severe course of IHD still not completely clear. In connection with the above mentioned observation, the study of various mechanisms, new risk factors and new approaches to therapy for such category of patients should be continued.

A moderate-stage hypercytokinemia without parallel rise of acute-phase mediators in patients with chronic IHD suggests the role of inflammatory pro-mediators in the development of IHD and this fact can be evaluated as a of the immune system participation in the pathogenesis of atherosclerosis [9].

It has been established that acute-phase proteins are the independent predictor of IHD development [10]. In our research it was confirmed that the concentration of fibrinogen and CRB was statistically significantly higher than in control group. Besides, there is a strong correlation between IL-6 and CBR levels and the degree of increase of acute-phase proteins in response to stimulation of inflammatory cytokines.

Significant increase of the level of immune inflammation markers in many cases associated with the alterations of blood cells rheological properties.

The degree of cytokine imbalance varies depending on the severity of IHD and correlates with acute-phase proteins, which allows the usage of laboratory diagnostic methods for objective measurement of IHD clinical course [11, 12].

Many studies have shown that during treatment on the traditional basis (aspirin, ACE inhibitors and statins) the levels of cytokines in the blood plasma were not essentially changed, except statins which demonstrates the decrease of CRB level [13, 14, 15, 16].

In our research, the inclusion of anti-inflammatory and immunomodulatory agents leads to a drop in markers of inflammation in the blood plasma as well as to improvement of the rheological properties of the blood comparing to another patients group treated only by the conventional therapy (without anti-inflammatory and immunomodulatory agents).

With this in mind, immuno-modulators and selective anti-inflammatory drugs are appropriate to include in the treatment in post-infarction angina with hypercytokinemia for optimization of pharmacotherapy.

Transparency of the study. *The study did not have sponsorship. The authors are solely responsible for the provision of the final version of the manuscript for publication.*

Declaration of financial or other relationships. *All authors participated in the conception and design of the study and in the writing of the manuscript. The final version of the manuscript was approved by all the authors. The authors did not receive a fee for the study.*

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ЗНАЧЕНИЕ ИНГИБИЦИИ ИНТЕРЛЕЙКИНА 6 ПРИ ЮВЕНИЛЬНОМ РЕВМАТОИДНОМ АРТРИТЕ

САЛАМЗАДЕ ГЮНАЙ ЗЕЛАБДИН кызы*, старший лаборант кафедры детских болезней №2 Азербайджанского медицинского университета, Азербайджан, AZ 1007, Баку, ул. Гасымзаде, 14, e-mail: mic_amu@mail.ru*

Реферат. ***Цель*** – оценка роли интерлейкина 6 в патогенезе и значение его ингибиции при ювенильном ревматоидном артрите, а также его участие в развитии таких внесуставных проявлений данного заболевания, как анемия, тромбоцитоз, остеопороз. ***Материал и методы.*** В исследовании приняли участие 54 ребенка. Средний возраст детей составил (11,1±0,6) года. 34 из них – дети с установленным диагнозом «ювенильный ревматоидный артрит» – составили 1-ю группу. Контрольную группу составили 20 практически здоровых детей. Были проведены клинический анализ крови, включающий определение уровней гемоглобина, числа эритроцитов, тромбоцитов, лейкоцитов, нейтрофилов, СОЭ; иммунологический анализ, включающий определение уровня С-реактивного белка, ревматоидного фактора, антител к циклическому цитруллинированному пептиду, уровень интерлейкина 6. В биохимическом анализе крови определяли уровень ионизированного кальция. Активность заболевания определялась по индексу DAS28 (Disease Activity Score), основанному на исследовании 28 суставов. Статистическая обработка цифрового материала была выполнена методами вариационного (Mann – Whitney, Moses), корреляционного (Spearman) и ROC-анализов в статистическом пакете IBM SPSS Statistics-21. ***Результаты и их обсуждение.*** Было обнаружено достоверное повышение уровня интерлейкина 6 в 1-й группе пациентов по сравнению с контрольной группой, установлена положительная корреляционная связь уровня интерлейкина 6 с числом тромбоцитов, понижением концентрации ионизированного кальция, понижением числа эритроцитов и уровня гемоглобина. Результаты подтверждают значимую роль интерлейкина 6 в патогенезе ювенильного ревматоидного артрита и его участие в развитии внесуставных проявлений. ***Выводы.*** Применение ингибиторов интерлейкина 6 позволяет достичь существенного прогресса в лечении ювенильного ревматоидного артрита и рассматривать ингибицию данного цитокина как одно из наиболее перспективных направлений фармакотерапии этого заболевания.

Ключевые слова: ювенильный ревматоидный артрит, цитокины, интерлейкин 6, ингибиция.

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