The Comparative description of aceclofenak and metoksikam influence on the balance of cytokines in patients with rheumatoid arthritis and chronic kidney disease

L. O. Zub*, S. W. Roborchuk

HSEE of Ukraine "Bukovinian State Medical University", Chernivtsi, Ukraine
*Corresponding author. E-mail: zublili@yandex.ru

Paper received 07.08.2016; Accepted for publication 20.08.2016.

Abstract. We investigated the effect of aceclofenac on the level of pro- and anti-inflammatory cytokines in patients with rheumatoid arthritis and chronic kidney disease. Influence of aceclofenac was compared with meloxicam. It is investigated to patients the content IL-1β, IL-10, TNFα, TGFβ1, MCP-1 in blood and urine. After two weeks of therapy with aceclofenac was revealed reduction IL-1β, TNFα levels in blood and urine in patients with RA and RA with CKD. Level of TGFβ1 is reduced. Decrease in the MCP-1 level in blood (in 1,5 times) and in urine (in 2 times) is revealed. Aceclofenac for complex treatment of patients with RA and CKD improves efficiency of treatment for these patients.

Keywords: *chronic kidney disease, pro - and antiinflammatory cytokines, rheumatoid arthritis.*

Introduction. Kidneys are often observed to be involved into pathological process at diseases of other organs and systems. For all this, there occur qualitatively definite changes of urinary sediment, combined with other clinical-laboratory signs of glomerular or tubular dysfunctions [1, 3].

Kidney pathology often arises as a result of the negative action of the methods of rheumatoid arthritis (RA) pathogenetic therapy, in particular non-steroid anti-inflammatory means (NSAIP) (medicamentously induced) [1, 5, 7].

Cytokines, low-molecular protein cellular regulators, being the mediators of the growth and differentiation of hemopoietic, lymphoid and mesenchymal cells, immune reactions and inflammation, play a great role in the pathogenesis of rheumatoid arthritis [2, 4, 6]. Besides, there are data, that interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNFα) sharply induce interleukin-6 (IL-6) synthesis, which influencing upon hepatocytes, causes hyperproduction of proteins of acute phase (C-reactive, fibrinogen and others), takes part in the development of periarthric osteoporosis, contributes to the synthesis of rheumatoid factor [8, 9, 10, 11]. Affection of kidneys in case of RA increases their sensitivity to NSAIP and nephropathy development risk.

Clinical-pathogenetic peculiarities of the progression of chronic kidney disease depending upon the methods of pathogenetic therapy of rheumatoid arthritis, as well as approaches to differential correction of pathogenetic program treatment of the patients suffering from rheumatoid arthritis with the presence of chronic kidney disease are not determined nowadays.

The aim of the research is to investigate the influence of aceclofenac on the level of pro- and anti-inflammatory cytokines in patients suffering from rheumatoid arthritis with the presence of chronic kidney disease.

Material and methods: 88 patients took part in the study: 45 patients with RA without CKD (23 patients were taking meloxicam as a part of a complex therapy – (group I of the examined patients) and 22 patients were taking aceclofenak – group II of the inspected patients; 43 patients with RA and CKD presence of stage I without nephrotic syndrome who were taking NSAIP as a part of a complex therapy (22 persons – meloxicam – group III of the examined patients); (21 patient – aceclofenak – group IV); and 20 healthy persons. All patients had II-III degree of RA activity and underwent a program cure according to the existing protocols.

Patients with availability of infection of the urinary tracts and genital organs were excluded from the research.

Aceclofenak has anti-inflammatory, analgesic and antipyretic action connected with a selective oppression of Cyclooxygenase 1 (COX-1) and COX-2. Meloxicam selectively inhibits COX-2, what regulates prostaglandins' synthesis in the focus of inflammation and to small degree reduces COX-1 activity taking part in synthesis of prostaglandins what protects mucous membrane of the stomach and regulates renal blood flow. Aceclofenak was administered in a dose of 100 mg twice a day after meal. Meloxicam was administered 1 tablet (15 mg) once a day when eating. After medicine it was recommended to take 250 ml of water.

Besides generally accepted standard methods of examination of the patients with nephrological and rheumatologic pathology, the content of IL-1β, IL-10, TNFα, transforming growth factor beta 1(TGFβ1), monocyte chemoattractant protein-1 (MCP-1) of the blood and urine by immune-enzymatic method using test-system ProCon IL-1β (Russian Federation) was studied in all patients, TGFβ1 level in the blood serum was determined using test-system DRG (USA), IL-10 – test-system "Vector Best" (Russian Federation), MCP-1 – by means of the test-system "Diaclone" (France), by means of analyzer Stat Fax-303. MCP-1 was defined in urine in order to determine the character of inflammation and its clinical course in kidneys.

This factor is the basic chemokin, which shows the formation of inflammatory infiltrate. The content of cytokines was investigated in the blood plasma and urine [9, 10, 11].

RA was diagnosed according to the Order of MPH of Ukraine of the 11.04.2014 N263 (unified clinical protocol of primary, secondary (specialized), tertiary (highly specialized) medical aid and medical rehabilitation "Rheumatoid arthritis") and recommendations of the American Collegium of Rheumatologists (ACR/EULAR) 2010 year. The availability of CKD was determined according to classification, adopted by the 2nd Congress of nephrologists of Ukraine (September, 24, 2005, Kharkiv).

The methods of statistical processing were conducted

on personal computer on the basis of processor Intel Celeron Cor2, using the program for carrying out medico-biological researches "BioStat". The average arithmetic selection (M), standard error (M) were calculated at statistical processing. Reliability of differences between indices under study was determined by means of Student's t- test.

Investigations were carried out in case of admission of a patient to hospital department before intake of administered NSAIP in a complex therapy and in 2 weeks of therapy.

The results and their discussion. During admission of a patient to the hospital the indices of cytokines before studying the previously mentioned NSAIP, were the following (fig.1,2): IL-1β content in patients with RA without CKD was 172,12 ± 3,17pg/ml, RA with CKD – 165,06 ± 3,21pg/ml.

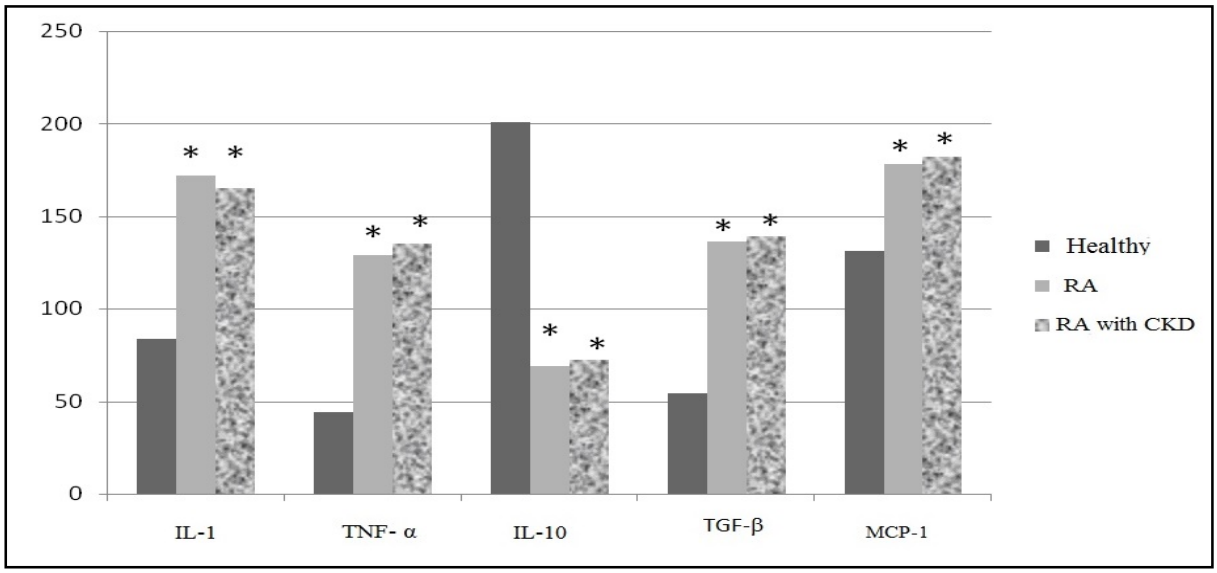

Fig. 1. Content of pro- and anti-inflammatory cytokines in the blood plasma of the patients suffering from RA with CKD before investigation.

It is reliably differed from indices of the group of healthy persons ($p < 0,05$). TNFα level in the blood was also reliably increased in all patients under study, 129,01 ± 7,11pg/ml and 135,15 ± 7,24pg/ml correspondingly, what also differed from normal values ($p < 0,05$) in both cases. IL-10 content was reliably decreased in both groups of patients – 68,99 ± 2,89pg/ml ($p < 0,05$) and 72,44 ± 3,02 pg/ml ($p < 0,05$) correspondingly. Thus, in this case all conditions for strengthening the production of the elements of acute phase of inflammation and maintenance RA activity were created. Usually, at CKD presence, a negative effect on kidneys is increased and all conditions for CKD progression in patients with RA are formed. In fig.1 it is also seen a reliable growth of prosclerotic factor TGFβ1 content in the blood of both groups of patients, that correspondingly constituted 136,33 ± 4,31pg/ml ($p < 0,05$) and 139,30 ± 3,92 pg/ml ($p < 0,05$), what also creates conditions for progression of the given nosologies with the development of irreversible changes in the form of fibrosis and sclerosis of tissues. The evident growth of MCP-1 in the blood of the patients under study in comparison with the group of healthy persons has been found, indicating the presence of the pronounced inflammation – 178,01 ± 8,05 pg/ml ($p < 0,05$) and 182,17 ± 8,14 pg/ml ($p < 0,05$) accordingly.

Changes of cytokines under study in the urine of patients, shown in fig. 2, demonstrate the availability of inflammatory changes in kidneys on the peak of RA exacerbation. So, IL-1β content was increased in the urine of both groups of patients, but its indices were reliably distinguished in patients with RA without CKD and with CKD availability in comparison with healthy persons – 22,88 ± 1,13 pg/ml ($p < 0,05$) and 87,56 ± 1,25pg/ml ($p < 0,05$) correspondingly. Difference of the data indices, in comparison between groups of the inspected patients, was also reliable, what manifested with greater IL-1β values in patients with RA, combined with CKD ($p < 0,001$). Trustworthy changes of TNFα and IL-10 in the urine were not detected. The level of TGFβ1 was reliably increased in the urine of patients suffering from RA with CKD presence – 4,57 ± 0,08 pg/ml ($p < 0,05$), that indicates to negative influence of the evident inflammation in case of RA and progression of CKD with evolutional development of irreversible changes in kidneys. MCP-1 was probably also increased in the urine only of the patients with CKD presence – 46,77 ± 1,56 pg/ml ($p < 0,001$). It indicates that RA activity induces strengthening of inflammation in renal parenchyma.

The following changes were determined while investigating cytokines in the blood of patients after a fortnight therapy with inclusion of the previously mentioned NSAIP (table 1).

IL-1β and TNFα indices reliably decreased in all groups under study compared to data before therapy what corresponded to ($p < 0,05$) in all groups. It is necessary to mention that reliably lower were IL-1β and TNFα indices using aceclofenak, what in comparison between II and I groups corresponded ($p < 0,05$) and between groups II and IV corresponded ($p < 0,05$) as well. Trustworthy distinctions between groups at IL-10 investigation were not detected. Changes while investigating TGFβ1 and MCP-1 and distinctions in groups were also reliable in comparison with the data before the treatment, but in comparison between II and I groups they corresponded

(p > 0,05), and between II and IV groups the distinctions were reliable (p < 0,05).

Somewhat other changes were determined when studying cytokines in the urine of the patients after fortnight therapy including the previously mentioned NSAIP (table 2).

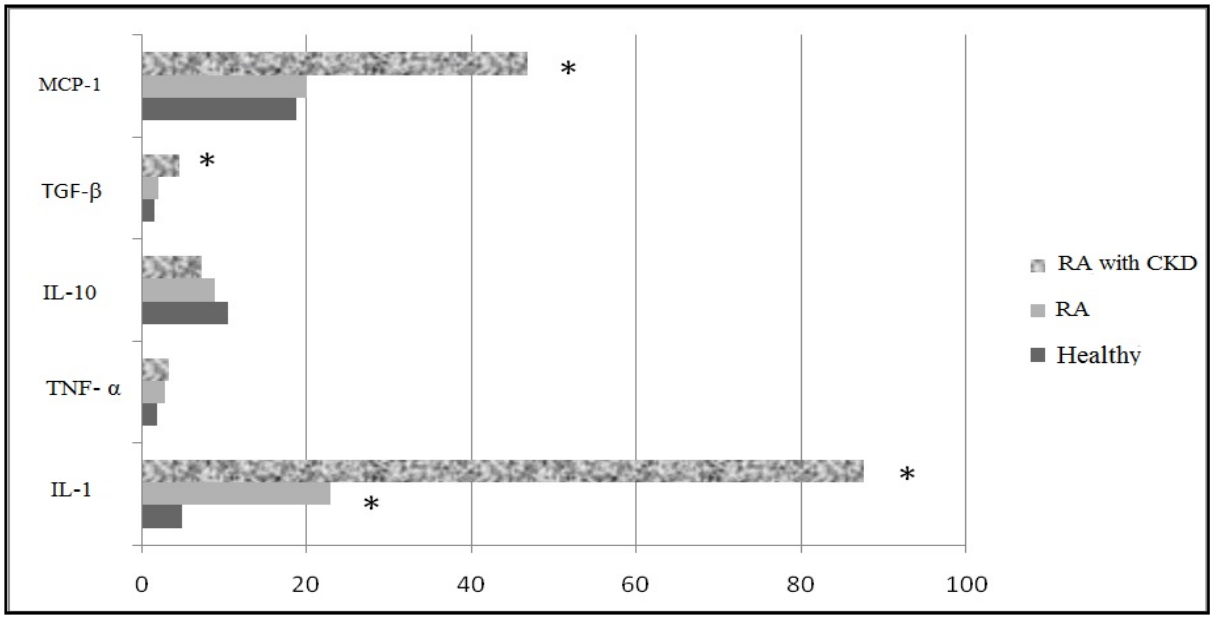

Fig. 2. Content of pro- and anti-inflammatory cytokines in the urine of patients suffering from RA with CKD I stage before investigation.

Table 1. Description of the content of pro- and anti-inflammatory cytokines in the blood plasma of the patients suffering from RA with CKD 1stage following fortnight therapy (M ± m, n)

Indices	Healthy (n = 20)	I group (n = 23)	II group (n = 22)	III group (n = 22)	IV group (n = 21)
IL-1$_\beta$ (pg/ml)	83,93 ± 2,03	124,28 ± 7,62*	101,23 ± 6,89*^	130,06 ± 7,03*	110,04 ± 6,06*#
TNFα (pg/ml)	44,02 ± 8,17	98,25 ± 6,23*	75,87 ± 6,37*^	111,25 ± 5,35*	99,13 ± 5,04*
IL-10 (pg/ml)	201,04 ± 3,42	93,89 ± 8,02*	105,34 ± 7,09*	91,33 ± 8,08*	101,09 ± 7,88*
TGFβ1 pg/ml)	54,49 ± 4,51	111,18 ± 4,99*	112,82 ± 3,31*	117,03 ± 5,29*	118,75 ± 5,31*
MCP-1 (pg/ml)	95,34 ± 9,05	122,04 ± 9,32*	119,14 ± 9,04	135,06 ± 8,22*	107,19 ± 9,07#
note to the table: * – p < 0,05 compared with healthy ^ – p < 0,05 compared with I group # – p < 0,05 compared with III group					

Table 2. Description of the pro- and anti-inflammatory cytokines content in urine of the patients suffering from RA with CKD stage I after fortnight therapy (M ± m, n).

Indices	Healthy (n = 20)	I group (n = 23)	II group (n = 22)	III group (n = 22)	IV group (n = 21)
IL-1$_\beta$ (g/ml)	4,95 ± 1,21	19,55 ± 2,02*	14,33 ± 2,12*	66,82 ± 2,21*	34,87 ± 2,26*#
TNFα (pg/ml)	1,98 ± 0,32	2,87 ± 0,24*	1,67 ± 0,36^	2,70 ± 0,12*	1,99 ± 0,11#
IL-10 (pg/ml)	10,57 ± 1,86	9,12 ± 1,33	9,94 ± 1,47	8,99 ± 1,52	9,87 ± 1,31
TGFβ1 pg/ml)	1,61 ± 0,07	3,87 ± 0,13*	2,81 ± 0,33*	3,89 ± 0,11*	2,12 ± 0,35*#
MCP-1 (pg/ml)	18,75 ± 22,05	28,07 ± 2,45*	29,11 ± 1,89*	30,02 ± 2,12*	19,85 ± 2,28#
note to the table: * – p < 0,05 compared with healthy ^ – p < 0,05 compared with I group # – p < 0,05 compared with III group					

Thus, a decrease of IL-1β content in urine of the patients of all groups under study was reliable in comparison with corresponding indices before the suggested treatment, what corresponded (p < 0,05) in all groups. It should be mentioned, that reliable distinctions (p < 0,05) were also detected in comparison with indices of this cytokine in III and IV groups. When studying TGFβ1 and MCP-1 their reliable decrease was also found as compared to the data before the treatment, what was in line with (p < 0,05) in all groups and more evident decrease of these cytokines' content was also revealed in patients with RA and CKD under the effect of aceclo-fenak (p < 0,05). In our opinion, this might be connected with mild and less traumatic action on kidneys of this NSAIP, what causes the need to continue

investigation in this direction.

Conclusions. Application of the proposed therapy including NSAIP aceclofenak of the new generation for multimodality treatment of patients suffering from RA with CKD availability enables to improve the efficacy of therapy of these patients by means of the evident improvement of indices of cytokine link of immunity of the blood and urine:

1. To decease the content of anti-inflammatory cytokines IL-1β of the blood ($p < 0,05$) and urine ($p < 0,05$), TNFα of the blood ($p < 0,05$) of patients with RA and with CKD presence;

2. To decrease the content of prosclerotic cytokine TGFβ1 of the blood ($p < 0,05$) and urine ($p < 0,001$) of the patients suffering from RA with CKD presence;

3. To influence positively upon monocyticmacrophage link of immunity, decreasing MCP-1 content of the blood (by 1,5 times) and urine (by 2 times) in patients with RA and CKD.

LITERATURE

1. Батюшин М.М. Клинические проявления и факторы риска поражения почек при ревматоидном артрите / М.М. Батюшин, Е.А. Выставкина // Фундаментальные исследования . – 2012. –№2. – С.249-252.
2. Боднарь И.А. Повышенная экскреция трансформирующего фактора роста-бета – ранний маркер нефропатии у больных сахарным диабетом I типа/ И.А. Боднарь, В.В. Климонтов, А.П. Надеев// Сахарный диабет.- 2007.-№2.- С. 14-18.
3. Зуб Л.О . Пат. 85183 Україна, МПК G01N 33/48 (2006.01). Спосіб ранньої діагностики уражень нирок у хворих на ревматоїдний артрит/ Зуб Л.О., Кулачек В.Т.; Заявник Буковинський державний медичний університет.- № заявки № u201306549 від 27.05.2013; опубл.11.11.2013, бюл. № 21.
4. Найда В.Т. Порівняльна характеристика показників трансформуючого фактору росту β_1 у хворих на ревматоїдний артрит в залежності від виду патології нирок / В.Т.Найда, Л.О.Зуб, Л.О.Гавриш // Клінічна та експериментальна патологія.-2011.- № 2(36),Ч.2.- С. 72-74.
5. Ребров А.П. Встречаемость хронической болезни почек и ее структура у больных ревматоидным артритом / А.П. Ребров, Е.В. Волошинова, М.А. Тяпкина // Клиническая нефрология. – 2011. - №6. – С. 32-35.
6. Серебренникова С.Н. Роль цитокинов в воспалительном процессе (сообщение №1) / С.Н. Серебренникова, И.Ж. Семинский // Сибирский мед. ж. - 2008. - №6. - С. 5-8.
7. Фоломеева. О.М. К проблеме определения внесуставных проявлений ревматоидного артрита / О.М. Фоломеева // Научно-практическая ревматология. – 2008. - № 2. – С. 74-82.
8. Чеботарева Р.В. Определение экскреции с мочой моноцитарного хемотаксического протеина-1 и трансформирующего фактора роста-β1 у больных хроническим гломерулонефритом как метод оценки процессов фиброгенеза в почне/ Н.В.Чеботарева, И.Н Бобкова, Л.В.Козловская, В.А. Варшавский, Е.П. Голицына// Клиническая нефрология.- 2010. - №3. – С. 48-53.
9. Sean Eardley K., Cockwell P. Macrophages and progressive tubulointerstitial disease/ K. Sean Eardley, P. Cockwell// Kidney Int. 2005. Vol. 68. P. 437–455.
10. Takamatsu N. Risk factors for chronic kidney disease in Japan: a communitybased study / N. Takamatsu, H. A be, T. Tominaga [et al.] // BMC Nephrol. 2009. Vol. 10. P. 34–44.
11. Tam P. W. K. U rinary monocyte chemoattractant protein-1 (MCP-1) is a marker of active renal vasculitis / P. W.K.Tam, J. S.Sauders, A.George // Nephrol. Dial. Transplant. 2004. Vol. 19. P. 2761–2768.

REFERENCES

1. Batiushyn M.M. Clinical manifestations and risk factors of the kidney damage at rheumatoid arthritis /M.M.Batiushyn, Ye.A.Vystavkina// Fundamental investigations. – 2012. – N 2, - C.249-252.
2. Bodnar I.A. Increased excretion of transforming growth-beta factor – early marker of nephropathy in patients with diabetes mellitus type I/ I.A.Bodnar, V.V.Klimontov, A.P.Nadeev // Diabetes mellitus. – 2007. – N 2. – C.14-18.
3. Zub. L.O.Pat. 85183 Ukraine, МПК G01N33/48 (200601). Method of early diagnostics of kidney affection in patients with rheumatoid arthritis / Zub L.O., Kulachek V.T., The applicant - Bukovinian state medical university.- application N u 201306549 of the 27.05.2013; publ.11.11.2013, bul. N 21.
4. Naida V.T. Comparative characteristics of indices of transforming growth β1 factor in patients with rheumatoid arthritis depending on the type of kidney pathology / V.T.Naida, L.O.Zub, L.O.Gavrysh // Clinical and experimental pathology. - 2011. – N 2 (36), part 2. – C. 72-74.
5. Rebrov A.P. Frequency of chronic renal disease and its structure in patients with rheumatoid arthritis / A.P.Rebrov, Ye.V. Voloshynova, M.A.Tiapkina// Clinical nephrology. – 2011. – N6. - C. 32-35.
6. Serebrennikova S.N. The role of cytokines in inflammatory process (report N1)/ S.N. Serebrennikova, I.Zh.Seminskii// Sibirskii med.jour. - 2008. – N6. - C.5-8.
7. Folomeeva O.M. To the problem of definition of extraarticular manifestations of rheumatoid arthritis/O.M.Folomeeva// Scientific-practical rheumatology. – 2008. – N2. – C.74-82.
8. Chebotareva R.V. Determination of excretion of monocytic chemotaxic protein-1 and transforming growth-β1 factor with urine in patients with chronic glomerulonephritis as a method of evaluation of fibrinogenesis processes in kidney/ N.V.Chebotareva, I.N.Bobkova, L.V.Kozlovskaya, V.A.Varshavskii, Ye.P.Golitsina// Clinical nephrology. – 2010. – N3. – C.48-53.
9. Sean Eardley K., Cockwell P. Macrophages and progressive tubulointerstitial disease/ K. Sean Eardley, P. Cockwell// Kidney Int. 2005. Vol. 68. P. 437–455.
10. Takamatsu N. Risk factors for chronic kidney disease in Japan: a communitybased study / N. Takamatsu, H. A be, T. Tominaga [et al.] // BMC Nephrol. 2009. Vol. 10. P. 34–44.
11. Tam P. W. K. U rinary monocyte chemoattractant protein-1 (MCP-1) is a marker of active renal vasculitis / P. W. K.Tam, J. S.Sauders, A.George // Nephrol. Dial. Transplant. 2004. Vol. 19. P. 2761–2768.

Сравнительная характеристика влияния ацеклофенака и мелоксикама на уровень про- и противовоспалительных цитокинов у пациентов с ревматоидным артритом с наличием хронической болезни почек

Л. А. Зуб, С. В. Роборчук

Аннотация. Исследовано влияние ацеклофенака на уровень про- и противовоспалительных цитоинов у пациентов с ревматоидным артритом с наличием хронической болезни почек. Действие ацеклофенака сравнивали с действием мелоксикама. Исследовано содержание ИЛ-1_{β} , ИЛ-10, ФНП$_{\alpha}$, ТФР$_{\beta 1}$, МСП-1 в крови и моче пациентов. После двухнедельной терапии с включением ацеклофенака определялось значительное снижение уровней ИЛ-1_{β} крові и мочи, ФНП$_{\alpha}$ крови, ТФР$_{\beta}$ крови и мочи исследуемых пациентов, а также значительное снижение уровня МСП-1 крови (в 1,5 раза) и мочи (в 2 раза). Ацеклофенак в комплексном лечении пациентов с ревматоидным артритом с наличием хронической болезни почек дает улучшает эффективность терапии.

Ключевые слова: *хроническая болезнь почек, про- и противовоспалительные цитокины, ревматоидный артрит.*