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PERSONALIZED TREATMENT OF PATIENTS WITH RHEUMATOID ARTHRITIS DEPENDING ON THE T-786C ENOS GENE PROMOTER POLYMORPHISM AND CONCOMITANT PATHOLOGY

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Abstract

High achievements in the search for effective means of treating rheumatoid arthritis, which allowed to achieve a reduction in the severity of the systemic immuno-inflammatory process, often cause the emergence of comorbid pathology. Given the frequent presence of arterial hypertension, abdominal obesity, and type 2 diabetes in patients with rheumatoid arthritis, it is advisable to use antihypertensive, hypolipidemic drugs, and metabolic therapy, including telmisartan, rosuvastatin, and L-arginine, in combination with basic therapy. Despite the indisputable success of pharmacotherapy in recent years, the prognosis for rheumatoid arthritis patients with the specified combined pathology remains disappointing. Therefore, improving the comprehensive approach to the treatment of rheumatoid arthritis with polymorbid pathology will improve the results of therapy, increase the duration of clinical remission and improve the patient's quality of life. ***Purpose:*** optimization of rheumatoid arthritis treatment depending on the *T-786C* polymorphism of the *eNOS* gene promoter and comorbid pathology. ***Materials and methods:*** 60 patients with rheumatoid arthritis with comorbid pathology and 20 practically healthy individuals were examined. Taking into account the presence of comorbid conditions, basic therapy with the use of telmisartan, rosuvastatin and L-arginine was prescribed. The general provisions on the procedure for conducting clinical research with human participation GCP (1996), the Helsinki Declaration of the World Medical Association on the ethical principles of conducting scientific medical research with human participation (1964-2013), the Council of Europe Convention on Human Rights and Biomedicine were observed (dated 04/04/1997), Order of the Ministry of Health of Ukraine № 1169 dated 09/26/2017 and on the procedure for conducting clinical trials of medicinal products and examination of clinical trial materials in accordance with Articles 7 and 8 of the Law of Ukraine "On Medicinal Products". Statistical processing was carried out using Microsoft Office Excel® 2007™, IBM SPSS Statistics® 23.0 applications. ***Results:*** After a personalized approach to the treatment of patients with RA with comorbid pathology, acute phase blood parameters significantly decreased. Namely, the level of CRP decreased by 34.89% ($p<0.001$), and RF by 1.4 times ($p<0.05$). A decrease in seromucoid content by 23.89% ($p<0.05$) and sialic test by 16.17% ($p<0.05$) was established in comparison with the data before treatment. The patient's overall assessment of pain according to VAS decreased by 16.7% ($p<0.05$), DAS28 by 1.38 times ($p<0.05$), and ESR level by 40.97% ($p<0.001$). It should also be noted the positive dynamics after treatment of the concentration of CRP and RF in the blood serum of patients with RA in the presence of the CC genotype - by 44.54% ($p<0.001$) and 43.19% ($p=0.001$), in carriers of the TT genotype - by 80% ($p<0.001$) and 77.82% ($p<0.001$) and in TC genotype carriers – by 47.01% ($p<0.001$) and 37.15% ($p<0.001$), respectively. VAS decreased in carriers of the TT genotype by 18.7% ($p<0.05$), in carriers of the TC genotype by 14.17% ($p<0.05$), and in carriers of the CC genotype by 22.64 % ($p<0.05$). Disease activity according to DAS28 decreased by 55.49% ($p<0.001$) in TT-genotype carriers, by 48.26% ($p<0.001$) in TC-genotype carriers, and in C C-genotype carriers by 30.1% ($p<0.05$). The ESR level after treatment decreased in TT-genotype carriers - by 44.06% ($p<0.001$), in TC-genotype carriers - by 44.43% ($p<0.001$) and in CC-genotype carriers - by 51.3% ($p<0.05$). ***Conclusions.*** Therefore, after the treatment, a decrease in the level of acute-phase indicators of inflammation was observed in all polymorphic variants of the *T-786C eNOS* gene, but it was the most significant in carriers of the TT genotype.

Keywords: rheumatoid arthritis, personalized treatment, *eNOS* gene promoter *T-786C* polymorphism, arterial hypertension, type 2 diabetes and abdominal obesity.

Introduction. Rheumatoid arthritis (RA) is the most common systemic disease of connective tissue, manifested by symmetrical chronic erosive-destructive progressive polyarthritis and immunoinflammatory damage to internal organs [1]. A cardinal feature of RA is the progressive impairment of joint function, which leads to a decrease in the quality of life [2]. Therefore, the prognosis in 1/3 of patients with RA is unfavorable and depends on early diagnosis and timely disease-modifying antirheumatic therapy (DMRT) [3]. On average, the life expectancy of patients with severe forms of RA is 7 years less than expected for men and 4 years for women [4] compared to the general population. Complete recovery of patients with RA is currently doubtful. Thus, according to the American College of Rheumatology (ACR), the frequency of complete remission with the use of the most powerful modern antirheumatoid drugs does not exceed 10%, and the radiological progression of the destructive process in the joints stops in only half of the patients, even when the reduction of clinical and laboratory manifestations of disease activity is achieved [5].

Ensuring adequate quality of life, increasing its duration, and reducing disability and mortality in patients with RA remains an unsolved problem [6]. Achieving this goal depends on timely diagnosis and rationally selected pharmacotherapy regimens [7], primarily with the use of disease-modifying antirheumatic drugs (DMARDs), glucocorticosteroids (GCs), and nonsteroidal anti-inflammatory drugs (NSAIDs) [8]. Pharmacotherapy does not always lead to remission, does not stop the progression of the disease, and at the same time has a number of side effects that cause the occurrence of concomitant diseases, burdening the clinical course and complicating the diagnosis of RA. Therefore, today there is a question regarding the optimization of RA treatment methods in combination with arterial hypertension (AH), abdominal obesity (AB), and type 2 diabetes mellitus (T2DM), which is poorly covered in domestic and foreign literature.

To achieve the optimal effect of RA treatment, it is necessary to adhere to a multidisciplinary approach, which consists in the use of pharmacotherapy, diet therapy, psychotherapy, physical therapy (PE), physiotherapy, sanatorium-resort treatment and surgical correction of joints while simultaneously increasing the patient's level of education about his disease [9].

Currently, early "aggressive" basic therapy is recommended, which quickly suppresses the immunoinflammatory process, prevents the development of cartilage destruction, as a result of which there is a high probability of achieving a stable remission [10].

Despite the introduction into clinical practice of biological agents (infliximab, etanercept, adalimumab, rituximab, anakinra, etc.) [11] and new HMPRPs (mofetil, mycophenolate), the "gold standard" of RA treatment remains MT [12]. According to the results of many randomized studies PROMPT, IMPROVED, DREAM, CAMERA, CAMERA-II, it has been confirmed that MT is a starting drug in the treatment of RA [13].

In addition to disease-modifying antirheumatic therapy (MDRT), the use of angiotensin II receptor blockers (ARBs), statins, and L-arginine can be recommended for the treatment of patients with RA in combination with high blood pressure, high blood pressure, and type 2 diabetes, since, in addition to antihypertensive effects, cholesterol-lowering properties and functional improvement endothelium, these drugs exert many pleiotropic effects, including anti-inflammatory and antithrombotic effects [14].

Therefore, determining the features of the course of RA against the background of comorbid pathology, taking into account genetic predictors, will allow to improve the prediction of the appearance of concomitant pathology, its early diagnosis and increase the effectiveness of treatment of patients with RA.

Materials and methods.

In the study, 60 patients with rheumatoid arthritis with comorbid pathology and 20 practically healthy individuals were examined. Medical care for patients with RA was provided in accordance with the Unified Clinical Protocol of Primary, Secondary (Specialized), Tertiary (Highly Specialized) Medical Care and Medical Rehabilitation "Rheumatoid Arthritis", approved by the Order of the Ministry of Health of Ukraine No. 263 of April 11, 2014 [15]; in the presence of hypertension - in accordance with the Order of the Ministry of Health of Ukraine No. 384 dated 05/24/2012 "On the approval and implementation of medical and technological documents on the standardization of medical care for hypertension" [16]; in the presence of type 2 diabetes mellitus - in accordance with the Order of the Ministry of Health of Ukraine No. 1118 dated December 21, 2012 "On the approval and implementation of medical and technological documents on the standardization of medical care for type 2 diabetes mellitus" [17].

The basic therapy of rheumatoid arthritis included: HMPRP - methotrexate ("Methotrexate" EBEWE Pharma Ges.m.b.H. Nfg. KG", Austria) at a dose of 10 mg per week, with a subsequent increase in the dose depending on effectiveness - by 5 mg every 2-4 weeks up to 20 mg/week; folic acid ("Folic acid", PJSC "Kyiv Vitamin Plant") in a half dose of MT no earlier than a day and no later than a day before taking this drug; GKS - methylprednisolone ("Medrol" Pfizer, Italy) in a dose of 20 mg with a gradual decrease lasting up to 1 month; NSAIDs - meloxicam ("Movalis" - "Boehringer Ingelheim International GmbH", Germany) in a dose of 15 mg intramuscularly with a transition to oral administration of 7.5 mg once a day for up to 1 month; calcium preparations ("Citra-calcemin" Bayer AG Spain/Germany) 1 tablet 2 times a day for 1 month.

Taking into account the presence of concomitant pathology, namely hypertension, hypertension and diabetes mellitus 2, in patients it was proposed to include antihypertensive therapy, a statin and L-arginine in the basic therapy: an angiotensin II receptor blocker (ARB) - telmisartan ("Telmisartan - TEVA" JSC Pharmaceutical Plant TEVA,) at a dose of 80 mg once a day in the morning under BP control; statin - rosuvastatin ("Roxera" KRKA, MD, Novo mesto, Slovenia) at a dose of 10 mg once a day in the evening after a meal, and for carriers of the *CC* genotype - up to 20 mg once a day in the evening after a meal; L-arginine hydrochloride ("Tivortin" LLC "Yuria-Pharm", Ukraine) 4.2%-100 ml intravenously with the transition to oral intake of L-arginine aspartate 5 ml 3 times a day for 1 month, and carriers of the *CC* genotype - up to 30 ml within 1 month. Short-term results were assessed after 30 days of therapy.

Statistical processing was carried out using Microsoft Office Excel® 2007™, IBM SPSS Statistics® 23.0 applications. Statistically significant changes in the dynamics of treatment with a normal distribution in the samples were determined by the Student's paired test or the non-parametric paired Wilcoxon T-test with unequal distribution.

The difference in the distribution of genotypes of the *T-786C* polymorphism of the *eNOS* gene in the control group and patients for the conformity of the distribution of genotypes to the Hardy-Weinberg law was tested using the $\chi 2$ test with 2 degrees of freedom, and in the control group - using the $\chi 2$ test with 1 degree of freedom, without using Yeats corrections. The difference was considered probable at $p<0.05$.

Research results and discussion.

Before treatment, the level of acute-phase indicators in the studied patients with RA with AH, AO and CID 2 were quite high. Since the common pathogenesis of these diseases mutually aggravates the course, provokes the appearance of extra-articular manifestations of RA, thereby worsening the patient's prognosis.

According to a study by American scientists, the main predictors of the development of hypertension are seropositivity for rheumatoid factor (RF), a large number of swollen joints and high indicators of disease activity according to DAS28 [18]. Therefore, the occurrence of hypertension in RA is due to persistent chronic inflammation, autoimmune, metabolic disorders and the use of antirheumatic drugs [19, 20].

The data of the meta-analysis showed that the risk of cardiovascular morbidity and mortality increases sharply already at the onset of RA in the presence of hypertension, AO, and type 2 diabetes [21, 22, 23], especially in women with RF seropositivity [24] and/or with hyperproduction of ACCP [25]. In addition, the presence of cardiovascular diseases (CVD) in patients with RA may determine the high activity of RA and prognostically low response to HMPRT [26].

Therefore, we chose this approach to the treatment of this cohort of patients. Which were confirmed by other studies. Namely, in the SAMERA-II and IMPROVED studies, it was established that with the combined therapy of MT and GCS in low doses (10 mg of prednisone), the remission rate was 72% and was achieved after 5 months, in contrast to MT monotherapy 61%, after 11 months [27].

When using GCS, the risk of hypertension, obesity, IR, and dyslipidemia arises due to a proatherosclerotic effect [28], but at the same time, they cause an anti-inflammatory effect, reducing the degree of RA activity, which paradoxically improves endothelial function [29].

Under the influence of our treatment, the content of acute-phase indicators of inflammation underwent significant changes (Table 1). In patients with RA with comorbid pathology, after the treatment, a decrease in the intensity of the inflammatory reaction was found, which had significant positive dynamics. It was found that before treatment, the level of CRP was increased 9.6 times compared to the control group ($p<0.001$). However, against the background of the therapy, the level of CRP decreased in patients with RA with hypertension, AO and type 2 diabetes - by 34.89% ($p<0.001$). The RF level exceeded the control level by 4.1 times ($p<0.05$-0.001). A 1.4-fold decrease in RF after treatment was observed in the studied group ($p<0.05$). A decrease in the content of seromucoid in relation to the initial values after treatment was established - by 23.89% ($p<0.05$), while their increase relative to the control by 4.53 times ($p<0.05$). The sial test decreased in patients with RA in combination with AO, hypertension and type 2 diabetes - by 16.17% ($p<0.05$) compared to the data before treatment (Table 1).

Table 1

Dynamics of acute-phase indicators of inflammation in the blood of patients with rheumatoid arthritis depending on comorbid pathology

Disease		CRP, mg/dl	RF, IU/ ml	ACCP, Unit/ml	Sial test, c.u.	Seromucoid, c.u.
Control, n=20		3,10±0,66	10,37±0,31	1,98±0,29	150,0±15,09	63,37±10,51
RA with AH, AO and T2DM, n=60	before treatment	29,74±3,24 p<0,001	42,27±4,78 p<0,001	125,75±16,39	258,30±9,37 p<0,001	343,30±23,81 p<0,001
	after treatment	22,08±2,45 p, p_1<0,001	29,91±3,67 p, p_1<0,05	116,91±17,16	222,35±9,11 p, p_1<0,05	277,10±18,6 p, p_1<0,05

Note. p- probability of differences in comparison with the control group; p1 is the probability of differences between indicators before and after treatment.

When determining the effectiveness of RA pharmacotherapy, it was established that the patient's overall assessment of pain according to VAS decreased by 16.7% ($p<0.05$) in RA patients with comorbid pathology. DAS28 after treatment decreased in this group by 1.38 times ($p<0.05$). The level of ESR exceeded the value of the control group by 8.34 times, and decreased after treatment in patients with RA in combination with AH, AO and T2DM - by 40.97% ($p<0.001$) (Table 2).

Table 2

Dynamics of disease activity and clinical response according to ASR in patients with rheumatoid arthritis with comorbid pathology

Disease		VAS, mm	DAS28	ESR mm/hour
Control, n=20				4,35±0,52
RA with AH, AO and T2DM, n=60	before treatment	79,80±1,92	6,25±0,19	36,30±3,45 p<0,001
	after treatment	68,40±1,93 p_1,<0,05	4,54±0,16 p_1<0,05	25,75±2,58 p, p_1<0,001

Note: p is the probability of differences compared to the control group; p1 is the probability of differences between indicators before and after treatment.

It should also be noted the positive dynamics after treatment of the concentration of CRP and RF in the blood serum of patients with RA in the presence of the *CC* genotype - by 44.54% (p<0.001) and 43.19% (p=0.001), however, it was less pronounced than in carriers of the *TT* genotype - by 80% (p<0.001) and 77.82% (p<0.001) and in carriers of the *TC* genotype - by 47.01% (p<0.001) and 37.15% (p<0.001) respectively. The level of the indicator of early diagnosis of RA by ACCP decreased only among carriers of the *TT* genotype by 12.1% without a significant difference among other polymorphic variants of the *eNOS* gene (rs 2070744) (Table 3).

Against the background of basic therapy with the addition of telmisartan, rosuvastatin and L-arginine, the level of the sialic test also decreased by 18.03% (p<0.05) - in carriers of the *TT* genotype, by 22.69% (p<0.05) - in carriers of the *TC* genotype and by 24.26% (p<0.05) in carriers of the *CC* genotype. It was established that the level of seromucoid decreased by 23.78%, 30.82% and 32.55% (p<0.001), respectively (Table 3).

Therefore, after the treatment, the decrease in the level of acute-phase indicators of inflammation in carriers of the *TT* genotype was the most significant.

Table 3

Dynamics of acute-phase indicators of inflammation after treatment in the blood of patients with rheumatoid arthritis depending on polymorphic variants of the eNOS gene (rs 2070744)

Genotypes of the eNOS gene in patients		CRP, mg/dl	RF, IU/ ml	ACCP, Unit/ml	Sial test, c.u.	Seromucoid, c.u.
Control, n=20		3,10±0,66	10,37±0,31	1,98±0,29	150,0±15,09	63,37±10,51
TT, n=27	before treatment	24,01±4,23 p<0,001	40,17±6,3 p=0,049	99,86±39,59	238,96±2,32 p<0,001	325,76±53,57 p<0,001
	after treatment	13,34±1,77 p, p_1<0,001	22,59±7,57 p<0,05 p_1<0,001	89,09±23,64 p_1<0,05	202,45±6,71 p, p_1<0,001	263,17±14,54 p_1<0,001
TC, n=23	before treatment	29,27±2,96 p<0,001	27,06±6,88 p=0,01	109,05±34,02	248,46±2,03 p<0,001	347,69±65,55 p<0,001
	after treatment	19,91±2,66	19,73±3,56 p_1<0,001	100,62±25,61 p_1<0,05	203,87±6,48 p, p_1<0,001	265,78±21,65 p_1<0,001
CC, n=10	before treatment	35,24±6,80 p<0,001	40,91±11,0 p=0,004	128,24±28,99	260,52±8,50 p<0,001	339,0±40,71 p=0,007
	after treatment	24,38±5,15 p,p_1<0,001	28,57±6,84 p=0,006 p_1=0,001	117,43±27,16 p_1<0,001	210,25±11,05 p <0,001	255,75±20,46 p_1 <0,001

Note: 2. p is the probability of differences in indicators with the control group; p1 is the probability of differences between indicators before and after treatment.

The effectiveness of the prescribed treatment complex is also confirmed by a decrease in the intensity of the pain syndrome according to the gradation of VAS, depending on the polymorphic variants of the *eNOS* gene (rs 2070744) (Table 4). It was found that this indicator decreased in carriers of the *TT* genotype by 18.7% (p<0.05), in carriers of the *TC* genotype - by 14.17% (p<0.05), and in carriers of the *CC* genotype - by 22.64% (p<0.05). A similar pattern was found for DAS28: a decrease in disease activity by 55.49% (p<0.001) in carriers of the *TT* genotype, by 48.26% (p<0.001) in carriers of the *TC* genotype, and with the weakest response to treatment in unfavorable *CC* genotype - by 30.1% (p<0.05). The level of ESR after treatment decreased without a statistically significant difference between the polymorphic variants of the *eNOS* gene (rs 2070744) (Table 4): in carriers of the *TT* genotype - by 44.06% (p<0.001), in carriers of the *TC* genotype - by 44.43 % (p<0.001) and in *CC* genotype carriers - by 51.3% (p<0.05), however, they exceeded the target levels by 4.14-5.49 times (p<0.001).

Table 4

Dynamics of pain syndrome intensity and rheumatoid arthritis activity index depending on polymorphic variants of the eNOS gene (rs 2070744)

Genotypes of the eNOS gene in patients		VAS, mm	DAS28	ESR mm/hour
Control, n=20				4,35±0,52
TT, n=27	before treatment	68,93±2,60	5,66±0,18	25,93±3,25 p<0,001
	after treatment	58,07±1,83 p_1<0,05	3,64±0,15 p_1<0,001	18,0±2,29 p, p_1<0,001
TC, n=23	before treatment	74,70±3,12	6,39±0,22	32,15±3,39 p<0,001
	after treatment	65,43±2,72 p_1<0,05 p_{TT}<0,05	4,31±0,22 p_1<0,001	22,26±2,29 p, p_1<0,001
CC, n=10	before treatment	81,25±5,26	5,88±0,28	36,13±5,65 p<0,001
	after treatment	66,25±4,54 p_1<0,05	4,52±0,17 p_1<0,001	23,88±3,01 p<0,001 p_1<0,05

Note: p is the probability of differences in indicators with the control group; p1 – the probability of differences between indicators before and after treatment; pTT is the probability of differences in indicators after treatment with carriers of the TT genotype.

Therefore, it was found that patients with RA in combination with AO, AH, and T2DM who are carriers of the mutant *CC* genotype had higher disease activity according to the DAS28, with the worst scores for pain and overall health status according to the VAS, which is supported by the data S. Amirdjanova et al. [30].

The best results in terms of achieving the ACR 20 criteria were observed in carriers of the *TT* genotype, in whom the activity of the disease decreased by 20% in all patients (100.0%), in carriers of the *TC* genotype - in 66.67%, and in carriers of the SS genotype only in a third of the studied patients (33.33%). However, 2 (8.70%) carriers of the *TC* genotype achieved a decrease in disease activity ACR 50, and ACR 70 was not observed for any of the polymorphic variants of the *eNOS* gene (rs 2070744) (Fig. 1).

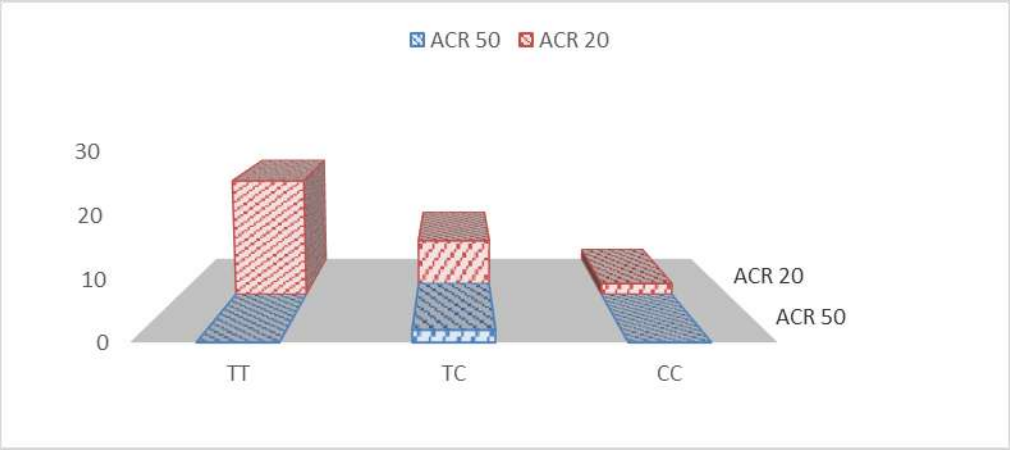

Figure 1. Distribution (%) of patients with rheumatoid arthritis taking into account polymorphic variants of the eNOS gene (rs 2070744) depending on the reduction of disease activity by the percentage of ASR 20 and ASR 50 responders after treatment.

Conclusion. A pathogenetically based complex treatment of rheumatoid arthritis combined with arterial hypertension, abdominal obesity and type 2 diabetes is proposed, with the addition of telmisartan, rosuvastatin and L-arginine to the basic therapy and a doubling of the dose of drugs for carriers of the *CC* genotype of the *T-786C* polymorphism of the *eNOS* gene promoter (rosuvastatin – up to 20 mg per day, L-arginine aspartate – up to 30 ml per day), which made it possible to increase the effectiveness of RA treatment, achieving a decrease in the severity of joint syndrome.

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