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CARDIOTROPIC INFLUENCE OF SYNTHETIC AND GENETICALLY-ENGINEERED SUPPRESSORS IN RATS WITH EXPERIMENTAL RHEUMATOID ARTHRITIS COMBINED WITH ARTERIAL HYPERTENSION

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Significant progress in rheumatoid arthritis pharmacotherapy is associated with the implementation of synthetic–derived immunosuppressors and genetically engineered (biological) drugs) into clinical practice. Arterial hypertension, like rheumatoid arthritis, is accompanied by producing a large amount of inflammatory cytokines, namely TNF–ά. The purpose of the work was to study the cardiotropic effects of leflunomide and etanercept against the background of experimental rheumatoid arthritis associated with arterial hypertension in rats. Experiments on mature adult, non-linear white rats found that leflunomide and etanercept did not affect the degree of hypertension against the background of adjuvant arthritis, but manifested an antihypertensive effect when used in adjuvant arthritis combined with arterial hypertension. Leflunomide leads to an increase in heart rate by 5–10.4% at different terms of observation, both against the background of adjuvant arthritis only and under the combined pathology conditions. Etanercept, when used against adjuvant arthritis, causes bradycardia but prevents the development of tachycardia, which is detected in untreated animals with a comorbid condition during manifestation and attenuation of the inflammatory process. The study findings may be relevant for development of new approaches to the treatment of rheumatic and cardiac pathology.

Keywords: leflunomide, etanercept, cardiotropic action, rheumatoid arthritis, hypertension, comorbid pathology

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Pathogenetic aspects of the onset and development of rheumatoid arthritis (RA) substantiate the pathogenetic basis of pharmacotherapy and determine the feasibility of using drugs of appropriate pharmacotherapeutic groups. Significant progress has been made in the pharmacotherapy of RA over the past decades, which is due to implementation of synthetic–derived immunosuppressants and genetically engineered (biological) drugs (GEBD) into clinical practice [2, 5].

The fundamental role in the pathogenesis of RA is played by TNFα, a pleiotropic cytokine with anti–inflammatory and immunomodulatory activity [3]. Among the GEBP, TNF–ά inhibitors were the first GEBP implemented into practice, and today they are ranked among this class drugs as "the first-line" drugs [2].

It is TNF–ά that is one of the major cytokines to determine the development of synovial inflammation and osteoblast-mediated bone destruction in arthritis. Therefore, TNF–ά is one of the main pharmacological targets for anticytokine therapy of RA and other inflammatory joint diseases.

The issues of the proinflammatory cytokines role in the origin and development of cardiac pathology are highlighted and discussed in the scientific periodicals [7, 8]. It is known that due to heart failure, the heart produces a large amount of inflammatory cytokine, namely TNF–ά, whose content and activity correlate with the degree of the left ventricle function impairment, the presence of changes in the myocardium, accompanied by a decrease in contractile function, can lead to apoptosis of cardiomyocytes with the direct link of this cytokine with the corresponding receptors on cardiomyocytes [3, 11].

These facts have caused the prediction that lowering the level of TNF–ά may have a positive effect on the functional status of the heart in the conditions of the heart failure and clinical manifestations of cardiac pathology. Experimental data and results of the limited clinical trial confirmed this result, however, the results of the large–scale controlled trials have shown a negative result and, in particular, worsening of state in patients with heart failure with the use of etanercept or infliximab [3].

Particularly acute is the issue of the safety and efficacy with the use of genetically modified and synthetic immunosuppressors against the background of combined pathology, in particular against the background of RA associated with hypertension. The side, namely, cardiotoxic effects of synthetic and genetically engineered immunosuppressants have not yet been sufficiently studied [7, 8].

Immunosuppressors can exhibit both general toxic effects [1] and cardiotoxicities, including the ability to increase the risk of hypertension, destabilization of blood pressure, increased preexisting hypertension, heart failure, heart rhythm disorders, etc. [3, 11]. There is no consensus among the world

researchers about the cardiac safety and cardio–efficacy of synthetic and biological immunosuppressors. For example, leflunomide (LF) in various RA patients may cause either hyper- or hypotension [5]. The effect of immunosuppressors on the cardiovascular system's condition against the background of RA combined with hypertension has not been studied [6, 12]. It is precisely because of the common pathogenesis link regarding the increase in the content and activity of proinflammatory cytokines in cardiac diseases associated with RA, namely, arterial hypertension (AH), that there is a prediction about the possibility of using immunosuppressors against the background of comorbid pathology of inflammatory nature.

Particular interest is drawn to the study on the efficacy of biological immunosuppressors that specifically block the activity of TNF–ά, against the background of both RA and comorbid cardiac pathology, in particular AH.

Quite effective in its implementation into clinical practice was the drug – TNF–ά inhibitor – Etanercept (ENB), which binds to biologically active TNF–ά (blocks its activity and prevents the latter from binding to the corresponding receptors). The drug regulates the activity of TNF–ά in RA, including – juvenile, psoriatic arthritis, psoriasis, ankylosing spondylitis [2].

The purpose of the work was to study the cardiotropic effect of leflunomide and etanercept against the background of experimental rheumatoid arthritis associated with hypertension in rats.

Materials and methods. The experiments were performed on mature non-linear white rats of both sexes with a starting weight of 168.5 ± 3.42 g, which were kept on a standard balanced diet in vivarium under free access to food and water at the temperature of 20–22^{o} C and relative humidity of 40–60%. The studies were carried out in compliance with the requirements of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986). After acclimatization (14 days) under normal diet and with free access to food and water in the laboratory room in special plastic cages of 7–8 specimens of similar sex in each random sample, white rats were divided into groups.

The first group included 20 intact animals that were kept in the laboratory room under the similar conditions and with the same duration as the animals of other experimental groups. The second group included white rats who were administered a complete Freund's adjuvant (AF) to simulate experimental RA (adjuvant arthritis – AA). The animals of the third group consisted of rats, which were induced AH. The animals of the fourth group were simulated a comorbid state – AH + AA. Animals of the fifth and sixth groups started treatment with LF and ENB 7 days after AF administration against the background of the formed AH. The seventh and eighth groups included rats with a comorbid condition, whose treatment with LF and ENB drugs, respectively, also began 7 days after the AF administration against the background of already formed hypertension. Therefore, animals that were only simulated AA (AA control), as well as AA rats (monopathology) treated with LF and ENB were not subject to salt loading at all. Simulation of hypertension was performed by means of salt loading, which was created by providing the animals with salt drinking (replacement of drinking water with saline solution – 1% sodium chloride solution) under the conditions of free access to it. Duration of hypertension development was 21 days [1, 9, 13]. Experimental RA was induced by subcutaneous injection of complete AF into the plantar part of the hind limb (left), which, according to the literature, is one of the most adequate agents capable of inducing the said pathological condition. The mechanism of developing AA induced by administration of complete AF, clinical symptoms, as well as the effects of drugs are most similar to those observed in humans with RA.

Comorbid pathology was simulated as follows: against the background of hypertension (on the 21st day from the start of AH model formation), the animals were singly administered complete AF. All animals were measured baseline BP and cardiac rate (CR) by a sphygmomanometric method with the Ugo Basile device (Italy). In rats subjected to salt loading, blood pressure was measured after 21 days. Animals that were not recorded an increase in blood pressure after 21 days from the beginning of the salt loading were not subject to the distribution into groups and were removed from the experiment under the relevant rules of euthanasia.

After randomization of rats with AH, the corresponding groups of animals were formed, each including almost the same number of rats of different sexes. LF was used as follows: the first three days at the dose of 15 mg/kg (shock dose), and then – daily at the dose of 1.5 mg/kg (therapeutic dose). The drug was injected through a special metal probe into the stomach in 1% starch suspension once a day (at 10 to 11 o'clock). Treatment of the animals was started 7 days after the AF administration (acute period of proper

AA). Duration of the animals' observation was 12 weeks from the start of the AH simulation, of which 21 days (3 weeks) was the formation of AH, then – 9 weeks after the AF administration against the background of the formed AH (including 8 weeks of treatment, which began 7 days after the AF administration). Administration of ENB was carried out subcutaneously at the dose of 4 mg/kg, which actually corresponds to the therapeutic dose for humans in terms of animals (rats). Administration of ENB was performed four times (once a week, in the same dose) – 7 days, 14 days, 21 days and 28 days after the complete AF administration.

Data Processing. The normality of distribution was assessed by the Shapiro–Wilk (W) criterion. Data are presented as the arithmetic mean and the standard error of the mean representativeness. The probability between the means in the two samples was determined using the Student test with normal distribution. Differences were considered statistically significant at a significance level of at least 0.05.

Results of the study and their discussion. No significant fluctuations in blood pressure in the animals of the intact group were observed. Experimental RA was accompanied by the development of hypertension, starting from the first days after the AF administration, which was characterized by an increase in blood pressure by 11–12% (table 1).

In animals with the salt load (third group) there was an increase in blood pressure by 17.9–27.0 % on the 7th-21st day of observation. It should be noted that with the increase in the term of salt load up to the 21st day the number of animals with an increase in blood pressure increased. Thus, 7 days after the AH model formation, 58.8% of white rats increased their blood pressure by 19%; blood pressure increased by 27% in 82.4% of animals on the 14th day of AH formation. The highest number of animals – 88.2% with elevated blood pressure by 17.9% was recorded on the 21st day.

It is this term that characterizes the actual presence of hypertension (the AH model) in white rats, as noted above. A significant increase in blood pressure in animals with salt loading (rats of the third group) was observed throughout the period of animal observation, however, starting from the 42nd–45th day from the start of daily use of 1% sodium chloride solution as a drink (free access of animals to drinking), a decrease in the degree of hypertension was recorded compared to the value registered on the 21st day.

Under the conditions of comorbid pathology modeling (administration of AF against the background of formed AH), there was no further increase of arterial pressure (AP) compared to the data recorded in animals with AH. Thus, complete AF does not lead to an increase in blood pressure against the background of the formed hypertension (i.e., AF does not lead to an increase in hypertension against the background of already developed disease; table 1). At the same time, during the acute period of the inflammatory process development and the period of its generalization (the 28th day after the AF administration), blood pressure remained significantly higher against the background of hypertension than that in intact animals, as well as in animals with AA alone.

According to the data in table. 1, LF did not lead to a decrease (normalization) of AP in AA rats, and throughout its duration, AP values remained similar to those observed in untreated AA animals (increased by more than 10%). The use of LF against the background of comorbid pathology, on the contrary, led to a significant decrease in blood pressure, the most significant during the period of AA decrement (the value of blood pressure in animals treated with LF decreased by 10% compared to the value in animals with a comorbid condition and reduced by 19.7 % compared to the value on the 21st day from the salt loading beginning.

Thus, the use of LF should be associated with continuous monitoring of blood pressure. In our opinion, against the background of AA alone, the use of LF should be combined with antihypertensive agents, which can only be confirmed or denied by performing a clinical trial.

With the use of ENB against AA, no significant increase in blood pressure was observed in rats, however, a rise in blood pressure of 4-8 % compared to baseline values was observed in this group (table 1). Thus, ENB did not lead to aggravated hypertension in the experimental RA. Under the conditions of comorbid pathology, ENB did not cause hypertension, but, on the contrary, significantly reduced blood pressure in rats during AA manifestation against the background of hypertension (recorded on the 21st day from the beginning of the salt loading) and reduced this index by 17% compared to values in untreated animals during the period of AA decrement (on the 60th day after AF administration). At the same time, blood pressure during the inflammation generalizing period remained higher than that of intact animals.

Table 1

Blood pressure (x ± SE, mm Hg) in rats using Leflunomide and Etanercept against adjuvant arthritis combined with arterial hypertension

Group, index	Term of observation, day^{Z}					
	Initial data•	7 (21+7)	14 (21+14)	28 (21+28)	42-45 (21+42)	56-60 (21+60)
Intact animals, n	92.2±4.2 20	93.4±1.4 20	90.7±2.8 20	92.2±1.4 20	93.2±1.8 20	94.7±1.2 20
AA n p (up to output values of the given group)	87.4±1.54 40	97.5±1.52 40 ≤0.05	97.9±1.70 40 ≤0.05	97.5±1.52 40 ≤0.05	97.2±1.50 40 ≤0.05	97.2±2.0 40 ≤0.05
AH (initial value – the 21st day), n	111.2±1.9* 33	107.0±1.4* 33	111.7±1.4* 33	108.2±2.5$^{\sharp}$ 33	101.6±2.0*$^{\sharp}$ 33	101.6±2.0*$^{\sharp}$ 33
AH+AA n	115.9±5.3* 25	106.4±2.8* 25	103.6±4.6* 25	100.2±3.7* 25	99.1±1.60 25	97.2±4.1 25
AA+LF n, p (up to output values of the given group)	87.4±1.16 15	97.4±3.35 15 ≤0.05	97.7±3.75 15 ≤0.05	95.7±2.37 15 ≤0.05	96.0±2.90 15 ≤0.05	98.1±4.0 15 ≤0.05
AA+ENB n, p (up to output values of the given group)	89.0±3.7 15	99.9±2.24 15 ≤0.05	96.4±3.7 15 ≥0.05	95.0±1.9 15 ≥0.05	92.7±3.4 15 ≥0.05	96.8±3.7 15 ≥0.05
AH+AA+ +LF, n	109.4±2.4* 15	106.4±2.8* 15	99.8±4.02$^{\sharp}$ 15	93.0±2.3$^{\sharp\Delta}$ 15	96.0±4.85 15	87.8±1.7*$^{\sharp\Delta\sigma}$ 15
AH+AA+ +ENB, n	115.9±5.3* 15	99.8±2.3$^{\sharp\Delta}$ 15	96.4±4.3$^{\sharp}$ 15	104.2±4.3*$^{\sharp\acute{a}}$ 15	102.3±3.0*$^{\sharp}$ 15	96.0±2.5$^{\sharp\acute{a}}$ 15

Notes (here and in the following table): 1. * – p≤0.05 - the index difference in the given observation period compared to its value in intact animals. 2. ♯ – p≤0.05 the index difference in the given observation period compared to the value in animals with hypertension on the 21st day. 3. Δ – p≤0.05 the index difference in the given observation period compared to the value in animals with hypertension for the same period of observation. 4. σ – p≤0.05 the index difference in the given observation period compared to the value in animals with combined pathology (AH + AA). 5. • – for the initial data, the values of the studied parameters, which were registered in animals on the 21st day from the beginning of the salt load, i. e., the value of blood pressure in animals with formed AH, were taken. 6. Z – the observation period is specified after the AF administration against the background of AH, in parentheses – the term of AH formation + the term starting from the AF administration).

Thus, the results of the studies showed that neither LF nor ENB enhanced hypertension caused by AF, and blood pressure during the action of these drugs remained elevated, similarly to the values in untreated animals against AA. Against the background of experimental RA in rats there was a significant increase in heart rate up to the 42nd–45th day after AF administration (table 2).

Statistically significant changes (decrease) in the cardiac rate should be noted 60 days after the induction of the inflammatory process. At the same time, the animals with formed AH against the background of continued saline solution consumption for more than 21 days showed a decrease in heart rate in the period from the 28th to the 81st day of observation (from the beginning of the salt loading), on average – by 12%. Thus, under the conditions of prolonged salt loading (more than 21 days), bradycardia develops in animals.

In the acute period of AA development against the background of AH and, particularly, in the period of AA decrement – on the 56th-60th days – significant changes in the cardiac rate (by 28.6%) were recorded compared to this index in animals with monopathology (AH), which were defined as tachyarrhythmia, and on the 42nd day of observation, they were also reliable compared to those observed in intact animals and testified to the 13.5% increase in the cardiac rate (table. 2). Significant changes (increase) of the cardiac rate by 5–10.4 % were caused by the synthetic immunosuppressor LF in different terms of its application against the background of AA.

The use of LF against the background of a comorbid condition was also accompanied by a significant (compared to the value in intact animals and rats with hypertension) increase in the cardiac rate, at the same time, the indicated reaction in this group was slightly weaker than that observed with the use of LF only against the background of AA. This fact can be regarded as a warning when applying LF both against the background of monopathology (AA) and in the comorbid state (AH + AA) and indicate the need to monitor the frequency and rhythm of heart rate and the use of appropriate therapies.

With the use of the ENB against the background of AA alone, a significant decrease in the cardiac rate was recorded (table 2), starting from the 28th day after AF administration and until the end of the observation period (the 60th day after AF administration) by 9.2–11.2 % compared to data recorded in animals with comorbid condition and intact rats.

Table 2

Cardiac rate (x ± SE, beats/min) in rats using Leflunomide and Etanercept against the background of experimental rheumatoid arthritis associated with hypertension

Group, index	Term of observation, day^{Z}					
	Initial data•	7 (21+7)	14 (21+14)	28 (21+28)	42-45 (21+42)	56-60 (21+60)
Intact animals, n	368.3±3.3 20	370.7±4.3 20	365.1±11.4 20	368.4±2.1 20	363.3±10.7 20	372.3±11.2 20
AA n	365.2±8.8 40	398.9±8.1* 40	396.7±8.7* 40	386.8±7.2* 40	354.1±6.4 40	340.1±9.8$^{*\sharp\sigma}$ 40
AH n	365.1±12.4 33	326.3±2.4$^{*\sharp}$ 33	321.5±5.3$^{*\sharp}$ 33	326.3±2.4$^{*\sharp}$ 33	325.7±9.8$^{*\sharp}$ 33	328.7±10.2$^{*\sharp}$ 33
AH+AA n	378.6±9.2 25	383.7±9.6$^{\Delta}$ 25	371.4±3.5$^{*\Delta}$ 25	367.1±9.2$^{\Delta}$ 25	385.0±3.5$^{\Delta}$ 25	422.6±10.2$^{*\sharp\Delta}$ 25
AA+LF n	378.6±4.76 15	-	398.5±7.8$^{*\sharp\Delta\sigma}$ 15	417.9 ±17.7$^{*\sharp\Delta\mathbf{6}}$ 15	417.8±6.3$^{*\sharp\Delta\mathbf{6}}$ 15	416.8±8.2$^{*\sharp\Delta}$ 15
AA+ENB n, p (up to output values of the given group)	361.1±6.2 15	363.0±8.4 15 ≥0.05	363.9±6.2 15 ≥0.05	326.7±7.4$^{*\mathbf{6}}$ 15 ≤0.05	320.6±9.4$^{*\mathbf{6}}$ 15 ≤0.05	326.±4.9$^{*\mathbf{6}}$ 15 ≤0.05
AH+AA+LF n	378.6±4.76 15	-	390.5±6.8$^{*\Delta\mathbf{6}}$ 15	380.0±5.8 $^{\Delta}$ 15	390.0±9.7$^{\Delta}$ 15	392.9±3.9$^{\sharp\Delta}$ 15
AH+AA+ENB, n	369.3±5.6 15	378.3±9.2$^{\Delta}$ 15	354.2±8.7$^{\Delta}$ 15	366.1±7.4$^{\Delta}$ 15	347.8±6.2$^{\sharp\mathbf{6}}$ 15	342.9±9.9$^{*\sharp\mathbf{6}}$ 15

In general, our results are consistent with those obtained by other researchers [3, 8, 11, 13]. ENB, immunosuppressant of biological origin, prevented the development of tachycardia, which was recorded in untreated animals with a comorbid condition during the manifestation and decrement of the pathological process [3]. At the same time, a significant decrease in the cardiac rate on the 42nd-60th day of observation compared to values in intact animals and in rats with a comorbid condition was reported with the use of ENB [4, 11]. Ability of LF and ENB to influence the rhythm and the cardiac rate of rats against the background of AH associated with AA indicates the feasibility of the rhythm and cardiac rate monitoring with the use of immunosuppressors [10, 13].

Conclusions

1. Leflunomide and etanercept do not affect the degree of hypertension against adjuvant arthritis, which is confirmed by a significant increase of blood pressure in rats (by more than 10%) similar to that observed in untreated animals with inflammatory process.

2. Leflunomide and etanercept have an antihypertensive effect when used against adjuvant arthritis combined with arterial hypertension, as evidenced by a decrease in the hypertension degree by 9–20 % and 17%, respectively, at different terms of inflammation development in rats compared to values in untreated animals with a comorbid condition.

3. White rats against the background of arterial hypertension combined with AA develop tachyarrhythmia, which is characterized by a significant increase in the cardiac rate by 28.6% compared to this index in animals with monopathology – arterial hypertension.

4. Leflunomide leads to an increase in the cardiac rate by 5–10.4 % at different terms of observation, both against the background of adjuvant arthritis only and under conditions of combined pathology. Etanercept, when used against adjuvant arthritis, causes bradycardia, but prevents the development of tachycardia, which is detected in untreated animals with a comorbid condition during the manifestation and attenuation of the inflammatory process.

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Реферати

КАРДІОТРОПНИЙ ВПЛИВ ІМУНОСУПРЕСОРІВ СИНТЕТИЧНОГО І ГЕННО-ІНЖЕНЕРНОГО ПОХОДЖЕННЯ У ЩУРІВ ЗА ЕКСПЕРИМЕНТАЛЬНОГО РЕВМАТОЇДНОГО АРТРИТУ, ПОЄДНАНОГО З АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ

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Істотний прогрес у фармакотерапії ревматоїдного артриту пов'язаний з впровадженням в клінічну практику імуносупресорів синтетичного походження і генно-інженерних (біологічних) препаратів. Артеріальна гіпертензія, як і РА, супроводжується продукцією великої кількості запального цитокіну, а саме - ФНП-ά. Метою дослідження було вивчення кардіотропного впливу лефлуномида і етанерцепта на тлі експериментального ревматоїдного артриту, асоційованого з артеріальною гіпертензією, у щурів. У дослідах на статевозрілих нелінійних білих щурах встановлено, що лефлуномід і етанерцепт не впливають на ступінь гіпертензії на тлі ад'ювантного артриту, але виявляють антигіпертензивний ефект при застосування на тлі ад'ювантного артриту, поєднаного з артеріальною гіпертензією. Лефлуномід призводить до зростання частоти серцевих скорочень на (5-10,4)% в різні терміни спостереження як на тлі лише ад'ювантного артриту, так і в умовах поєднаної патології. Етанерцепт при застосуванні на тлі ад'ювантного артриту викликає брадикардію, але запобігає розвитку тахікардії, що реєструється у нелікованих тварин з коморбідним станом в період маніфестації і згасання запального процесу. Результати досліджень можуть мати значення для розробки нових підходів в лікуванні ревматичної та кардіальної патології.

Ключові слова: лефлуномід, етанерцепт, кардіотропна дія, ревматоїдний артрит, артеріальна гіпертензія, коморбідна патологія.

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КАРДИОТРОПНОЕ ВЛИЯНИЕ ИММУНОСУПРЕССОРОВ СИНТЕТИЧЕСКОГО И ГЕННО-ИНЖЕНЕРНОГО ПРОИСХОЖДЕНИЯ У КРЫС ПРИ ЭКСПЕРИМЕНТАЛЬНОМ РЕВМАТОИДНОМ АРТРИТЕ, ОБЪЕДИНЕННОМ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ

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Существенный прогресс в фармакотерапии ревматоидного артрита связан с внедрением в клиническую практику иммуносупрессоров синтетического происхождения и генно-инженерных (биологических) препаратов. Артериальная гипертензия, как и РА, сопровождается продукцией большого количества воспалительного цитокина, а именно – ФНО–ά. Целью исследования было изучение кардиотропного влияния лефлуномида и этанерцепта на фоне экспериментального ревматоидного артрита, ассоциированного с артериальной гипертензией, у крыс. В опытах на половозрелых нелинейных белых крысах установлено, что лефлуномид и этанерцепт не влияют на степень гипертензии на фоне адъювантного артрита, но проявляют антигипертензивный эффект при применение на фоне адъювантного артрита, объединенного с артериальной гипертензией. Лефлуномид приводит к росту частоты сердечных сокращений на (5-10,4)% в разные сроки наблюдения как на фоне только адъювантной артрита, так и в условиях сочетанной патологии. Этанерцепт при применении на фоне адъювантного артрита вызывает брадикардию, но предотвращает развитие тахикардии, что регистрируется у нелеченных животных с коморбидным состоянием в период манифестации и угасания воспалительного процесса. Результаты исследований могут иметь значение для разработки новых подходов в лечении ревматической и кардиальной патологии.

Ключевые слова: лефлуномид, этанерцепт, кардиотропное действие, ревматоидный артрит, артериальная гипертензия, коморбидная патология.

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