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STUDY OF CHONDROPROTECTIVE PROPERTIES OF INTERLEUKIN-1 RECEPTOR ANTAGONIST

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Osteoarthritis is one of the most widespread diseases, represents a medical and socio-economic problem and is one of the first places among the causes of long-term disability of the population in the world. Cytokine mechanisms of osteoarthritis development are attracting more and more attention.

***The aim** of the study was to determine the chondroprotective and anti-inflammatory properties of the original recombinant interleukin-1 (IL-1) receptor antagonist (ARIL-1) raleukin on the model of systemic steroid osteoarthritis (SSO) in rats.*

Materials and methods. The SSO model was reproduced in a modified form by intramuscular three-time administration of dexamethasone at a dose of 7 mg/kg with an interval of one week. Raleukin was injected subcutaneously in a conditionally effective dose of 3 mg/kg for anti-inflammatory activity, and glucosamine (GA) orally in a dose of 50 mg/kg (ED_{50} for anti-inflammatory activity). Starting from the 28th day of the study and for 4 weeks, the study objects were introduced by the appropriate route once a day.

***Result**. The results of the experiment show that clinical signs of damage to the locomotor system appeared in all animals after three administrations of dexamethasone. Later and before the end of the experiment, a typical clinical picture of the development of SSO was observed, which was confirmed by the results of the study of biochemical markers (mainly in blood serum) of the state of the connective tissue of the experimental animals.*

Significant changes in the functional status of the animals were noted in rats with SSO who received raleukin starting from the second week of administration. In rats, motor activity increased, tolerance to physical exertion increased, joint condition visually normalised, and appetite increased. When the reference drug GA was administered, the functional state of the animals differed from the control pathology group to a somewhat lesser extent. Besides, raleukin did not reliably differ from GA in its effect on biochemical parameters characterising the state of connective tissue and the content of its main metabolites in the blood serum of rats with steroid osteoarthritis.

***Conclusions**. In the model of systemic steroid osteoarthritis, raleukin contributed to the improvement of functional indicators of the condition of animals and the normalisation of their body weight; namely, it moderately reduced the content of all markers of connective tissue metabolism in the blood serum of animals, especially chondroitin sulfates and sialic acids, which can be explained by the systemic nature of its effect. In terms of its effect on the level of the main metabolites of connective tissue in the blood serum of rats, raleukin prevailed over glucosamine hydrochloride. Thus, the analysis of biochemical data against the background of experimental osteoarthritis allows us to draw a conclusion about the high chondroprotective and anti-inflammatory potential of the recombinant IL-1 receptor antagonist*

***Keywords**: interleukin-1 receptor antagonist, raleukin, osteoarthritis, chondroprotective effect, anti-inflammatory effect*

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1. Introduction

Osteoarthritis is one of the most widespread diseases, represents a medical and socio-economic problem and is one of the first places among the causes of long-term disability of the population in the world [1, 2]. According to the WHO, osteoarthritis affects 6.4–12 % of the world's population. The total number of osteoarthritis patients in Ukraine exceeds 1,300,000 people. At the age of over 60, various manifestations of osteoarthritis are observed in almost every person [3].

Osteoarthritis is a chronic progressive joint disease of unknown etiology, characterised by cartilage degeneration and structural changes in the subchondral bone, as well as overt or hidden moderate synovitis. Osteoarthritis is a polyetiological disease. Trauma, dysplasia and inflammation are the main causes of the development of degenerative processes in the joint. There are primary and secondary osteoarthritis. Primary osteoarthritis is the premature ageing of previously healthy cartilage as a result of excessive mechanical and functional stress. Secondary osteoarthritis is damage to the cartilage of joints that were previously exposed to pathological influences (trauma, arthritis, gout, endocrine disorders, etc.). The main role is played by changes in the articular surfaces of the bone, fibrous-scle-

rotic changes in the synovial membrane, and reactive synovitis. Changes in the articular surface of the bone include microcirculation disorders and compensatory bone growth along the periphery of the articular surfaces. Reactive synovitis is a consequence of irritation of the synovium by pieces of necrotic cartilage. Sometimes, there is hypertrophy of synovial villi with cartilaginous or bone metaplasia. Currently, the role of autoimmune processes that stimulate catabolic processes and damage to articular cartilage has been proven in the pathogenesis of osteoarthritis [1, 3].

Cytokine mechanisms of osteoarthritis development are attracting more and more attention. It is known that pro-inflammatory interleukin-1 (IL-1) in the cells of bone and cartilage tissue stimulates the production of proteases by chondrocytes, increases the production of prostaglandin E_2, and increases the proliferation of synovial fibroblasts and chondrocytes. In muscle tissue, under the influence of IL-1, muscle proteolysis occurs, and prostaglandin E_2 synthesis is stimulated. Under the influence of IL-1, connective tissue cells simultaneously increase the synthesis of collagen and collagenase, as well as other enzymes, namely neutral protease and metalloproteinase [4, 5]. By stimulating the proliferation and functional activity of both osteoblasts and osteoclasts, IL-1 can, on the one hand, enhance the processes of formation of connective and bone tissue and, on the other hand, promote the resorption of cartilage and bone [6–9]. Presumably, IL-1 is also able to intervene in the exchange of glycosaminoglycans [10–13]. That is, it can be assumed that the IL-1 receptor antagonist (ARIL-1), having anti-inflammatory properties already, may also have chondroprotective properties.

Determination of the chondroprotective and in-depth study of anti-inflammatory properties of the original recombinant IL-1 receptor antagonist raleukin on the model of systemic steroid osteoarthritis (SSO) in rats became the aim of this study.

2. Planning (methodology) of research

To achieve the goal, taking into account the main principles of the concept of Quality by design (QbD), in this study, it was necessary to reproduce a model of connective tissue damage – SSO, as well as to study the effect of the researched agent Raleukin (an anti-cytokine agent) in comparison with a classic chondroprotector on the course of this model pathology according to indicators of systemic and local clinical and biochemical changes in the body (Fig. 1).

The model of systemic steroid (dexamethasone) osteoarthritis was chosen by us because the resulting systemic and local pathological changes, namely, degeneration of joints (cartilage and bones) and the inflammatory process, are close to the clinical picture of degenerative diseases of connective tissue in humans [14–16].

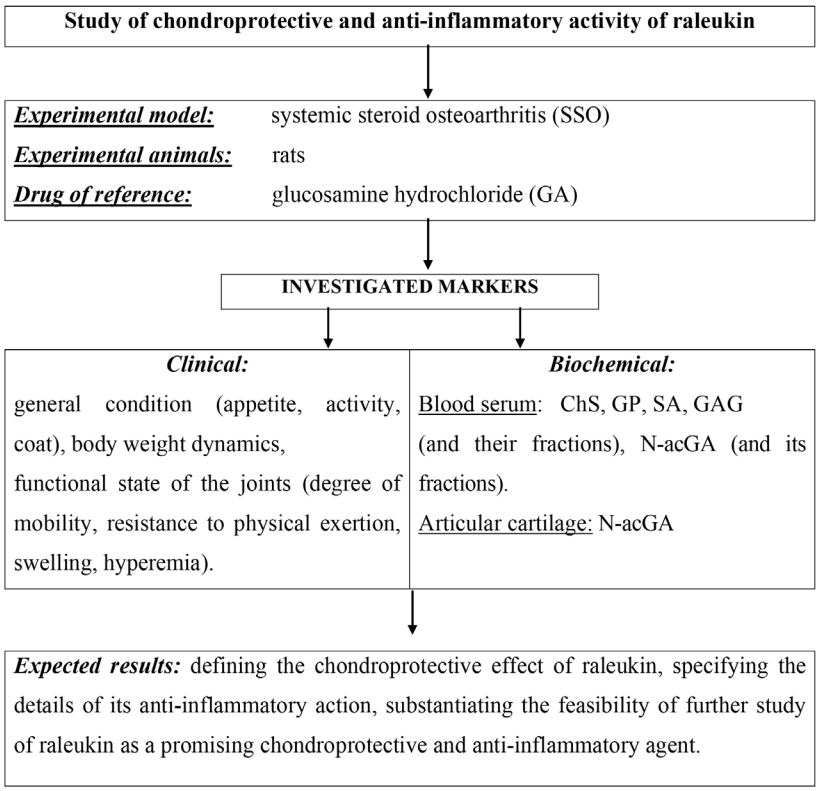

Fig. 1. The structure of the planned study

3. Materials and methods

The study was conducted in 2010–2011 at the Central Scientific Research Laboratory of the National University of Pharmacy, which is certified by the State Pharmacological Center of the Ministry of Health of Ukraine (certificate No. 21 dated April 30, 2009).

The animals were kept under standard conditions in the vivarium of the Central Scientific Research Laboratory of the National University of Pharmacy according to the GLP standards. The research was conducted in accordance with the National "General Ethical Principles of Animal Experiments" (Ukraine, 2001), which correspond to the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1985). Painful procedures (surgery, euthanasia, organ removal) were performed under anesthesia (intraperitoneal sodium thiopental at a dose of 80 mg/kg of body weight or sodium ethaminal at a dose of 40 mg/kg). Compliance with ethical standards was confirmed by the bioethics commission of the National University of Pharmacy (Protocol No. 3 dated March 16, 2011).

The study of the chondroprotective and anti-inflammatory properties of raleukin (solution for injections, "RESBio") was carried out on 50 rats weighing 250–300 g. The standard chondroprotector glucosamine hydrochloride (GA) (oral powder, "Protein Chemicals") was chosen as the comparison drug [14, 15]. Raleu-

kin (freeze-dried protein) was injected subcutaneously in a conditionally effective dose of 3 mg/kg for anti-inflammatory activity, GA – orally in a dose of 50 mg/kg (ED_{50} for anti-inflammatory activity).

The SSO model was reproduced in a modified form by intramuscular three-time administration of dexamethasone (solution for injections, 4mg/ml; "KRKA") at a dose of 7 mg/kg with an interval of one week [15, 16]. To assess the degree of activity of the pathological process, for the 4th week of the study, part of the animals of the control group (10 heads) were removed from the experiment by decapitation under ether anesthesia in order to obtain biological material for biochemical studies.

Starting from the 28th day of the study and for 4 weeks, the study objects were introduced by the appropriate route once a day. During the experiment, clinical observation of the animals was carried out, and the functional state of the rats' joints was monitored (the degree of mobility, resistance to physical exertion, swelling, hyperemia). After the end of administration of the studied drugs (on the 56th day of the experiment), the animals were removed from the experiment, and biomaterial was collected for clinical and biochemical studies.

In the course of the study, the following biochemical indicators were determined: the content of sialic acids (SA) in blood serum according to the Hess method [17], the content of glycoproteins (GP) in blood serum by the reaction with molybdenum-sulphuric acid reagent according to the Steinberg-Dotsenko method, the content of chondroitin sulfates (ChS) in blood serum according to L. I. Slutsky [17], the content of the total amount and fractions of glycosaminoglycans (GAG) in blood serum according to the reaction of precipitation with a solution of resoxime according to the method of M. R. Shtern et al. in a modification [18], as well as the content of endogenous N-acetylglucosamine (N-acGA) in blood serum (total, free and bound fractions) and articular cartilage tissues by the reaction of the interaction of hexosamine with acetylacetone and Ehrlich's reagent in an alcoholic medium [19, 20]. The studied indicators were taken into account in the form of initial data, for which intact animals were used, on the 28th (for the control pathology group) and 56th day of the study.

The Student's t-test with Bonferroni correction was used for statistical processing of the results presented as mean±standard error of the mean.

4. Results

The results of the experiment show that clinical signs of damage to the locomotor system appeared in all animals after three administrations of dexamethasone. First of all, the animals were lethargic and inactive. Swelling of the knee joints, a decrease in the amplitude of movement, poor mobility, and a decrease in tolerance to physical exertion were observed. In addition, a decrease in appetite and a wool coat disorder was noted. A typical clinical picture of the development of SSO was observed in the future and until the end of the experiment.

Significant changes in the functional status of the animals were noted in rats with SSO who received raleukin starting from the second week of administration. In rats, motor activity increased, tolerance to physical exertion increased, joint condition visually normalised, and appetite increased. When the reference drug GA was administered, the functional state of the animals differed from the control pathology group to a somewhat lesser extent.

Against the background of the introduction of dexamethasone, there was a constant increase in body weight, which was statistically significant compared to the initial data and indicators of the intact group (Table 1).

Table 1

Dynamics of body weight of rats under the influence of raleukin and glucosamine hydrochloride against the background of the development of systemic steroid osteoarthritis (*M*±*m*)

Groups of animals	Body weight, g			
	Original data	14 days	28 days	56 days
Intact control (*n*=10)	261.2±2.9	270.1±3.5	276.5±4.9*	287.4±5.1*
Control pathology (*n*=20)	263.1±3.5	273.7±4.8	290.8±5.1*	322.,3±5.1*/**
Raleukin 3.0 mg/kg (*n*=10)	262.1±3.0	272.0±3.8	280.9±4.3*	302.9±2.9*/**#
Glucosamine hydrochloride 50.0 mg/kg (*n*=10)	259.7±2.7	270.3±2.4	283.4±3.5*	306.6±3.6*/**#

*Note: statistically significant differences (p≤0.05): * – with original data; ** – with a group of intact animals; # – with the control pathology group*

These changes correspond to the peculiarities of the pharmacodynamics of glucocorticosteroids. The maximum indicators of body weight (increase on average by 86.2 g, or by 22.4 %) were observed in the control pathology group on the 56th day of the experiment. Under the influence of the studied drugs, the increase in body weight of animals was probably less than in untreated animals. Thus, in the case of using raleukin, the weight increased on average by 40.8 g (15.6 %) against 46.9 g (18.1 %) against the background of GA.

Indicators of the main metabolites of connective tissue, such as ChS, GP and SA were parameters for evaluating the degree of chondroprotective activity of Raleukin. It should be noted that among them, the level of ChS is of the greatest importance in the development of SSO, since it is the main GAG of the articular cartilage matrix. Compared to ChS, indicators such as GP and SA are less specific and, to a greater extent, reflect acute-phase pathological processes (especially inflammation) in the connective tissue. Data on the content of the main metabolites of connective tissue in the blood serum of rats with SSO under the influence of experimental therapy are shown in Table 2.

After the administration of dexamethasone in rats of the control group, a significant increase in the content of all metabolites in comparison with the intact control group occurred as of the 28th day of the experiment, which confirms the development of a pathological process in the connective tissue in all studied animals. In the future, this trend persisted, and 56 days after the start of

the study, the level of ChS and GP was increased by 1.4 and 1.6 times, respectively, compared to intact animals. The SA content decreased slightly and was equal to 5.0 mmol/l, which is 1.4 times more compared to the indicator of the intact group (Table 2).

Under the influence of raleukin, a moderate decrease in the content of all markers of connective tissue metabolism in the blood serum of animals was observed, especially ChS and SA, where probable differences were observed compared to the control pathology group. So, the level of ChS decreased by 15 %, GP – by 19 %, and SA – by 22 % (Table 2). This is obviously related to the systemic nature of raleukin's effect on metabolic processes in the connective tissue.

Table 2

The content of the main metabolites of connective tissue in the blood serum of rats with experimental osteoarthritis under the influence raleukin and glucosamine hydrochloride (*M*±*m*)

Groups of animals	Chondroitin sulfates, g/l	Glycoproteins, g/l	Sialic acids, mmol/l
Original data			
Intact control (*n*=10)	0.302±0.018	2.65±0.14	3.49±0.17
28 days			
Control pathology (*n*=10)	0.418±0.025*	4.03±0.29*	5.24±0.32*
56 days			
Control pathology (*n*=10)	0.434±0.026*	4.22±0.39*	5.03±0.20*
Raleukin 3.0 mg/kg (*n*=10)	0.367±0.015#	3.28±0.29	4.06±0.27#
Glucosamine hydrochloride 50.0 mg/kg (*n*=10)	0.343±0.030#	3.45±0.31	4.37±0.39

*Note: statistically significant differences (p≤0.05): * – with original data; # – with a control pathology group*

When using GA, the dynamics of connective tissue metabolism indicators in the blood serum of animals according to the ChS indicator was somewhat more marked than under the influence of raleukin, according to the GP and SA indicators, it was slightly less marked, in comparison to ARIL-1, but no probable differences between the corresponding indicators in both treated groups were recorded. At the same time, the SA content in rats treated with GA probably did not differ from the rate of untreated rats, in contrast to animals treated with raleukin. So, in terms of its effect on the content of the main metabolites of connective tissue in the blood serum of rats with SSO, raleukin did not reliably differ from GA and even tended to a better effect.

The most important biochemical indicator characterising the intensity of pathological changes in animal joint tissues with the SSO model is the total amount and fractions of GAG in blood serum. It is known that normally, the main fraction of GAG is hyaluronate and chondroitin-6-sulfates. As the disease progresses, the ratio of fractions of this marker undergoes specific changes, as a result of which the amount of GAG increases due to an increase in the content of chondroitin-4-sulfates since it is this GAG in the largest quantities that is contained in the cartilage matrix and is released from it as a result of destruction [21, 22].

With the increasing severity of the course of the pathological process, an increase in the content of highly sulfated fractions of GAG, represented mainly by keratan sulfate, is observed. That is, the analysis of the ratio of different fractions of GAG, as well as the content of their total amount in blood serum, allows us to assess the course of osteoarthritis and the effectiveness of treatment. The results of changes in the fractional composition and total content of GAG in the blood serum of rats with SSO under the influence of raleukin are shown in Table 3.

Analysis of Table 3 data shows that, normally, in intact animals, the fraction of hyaluronates and chondroitin-6-sulfates accounts for 60 % of the total amount of GAG, the fraction of chondroitin-4-sulfates – 33.5 %, and the highly sulfated fraction of GAG – 6.5 %. During the development of pathology (28 days of the experiment), not only was there a significant increase in the amount of GAG compared to intact animals, but also a change in the percentage ratio of fractions - chondroitin-4-sulfates already accounted for 40 % of the total amount of GAG. During the further development of the model pathology (56 days of the experiment), this tendency persisted. The total amount of GAG compared to the initial data increased by 1.4 times, mainly due to chondroitin-4-sulfates, which accounted for more than 43 % of the total amount of GAG.

Table 3

Fractional composition and total content of glycosaminoglycans in blood serum of rats with experimental osteoarthritis under the influence of raleukin and glucosamine hydrochloride (*M*±*m*)

Groups of animals	Content of glycosaminoglycan fractions, g/l			Total content of glycosaminoglycans, g/l
	hyaluronates and chondroitin-6-sulfates	chondroitin-4-sulfate	highly sulfated glycosaminoglycans	
original data				
Intact control (*n*=10)	0.195±0.013	0.109±0.008	0.021±0.002	0.325±0.023
28 days				
Control pathology (*n*=10)	0.236±0.022*	0.176±0.016*	0.023±0.002	0.435±0.040*
56 days				
Control pathology (*n*=10)	0.233±0.014	0,195±0.012*	0.025±0.002	0.453±0.028*
Raleukin 3.0 mg/kg (*n*=10)	0.199±0.011	0.152±0.009*#@	0.024±0.001	0.375±0.021#
Glucosamine hydrochloride 50.0 mg/kg (*n*=10)	0.207±0.012	0.126±0.007#	0.020±0.002#	0.354±0.021#

*Note: statistically significant differences (p≤ 0.05): * – with a group of intact animals; # – with a control pathology group; @ – with a group of glucosamine hydrochloride*

The level of highly sulfated GAGs during the development of SSO had a slight upward trend and did not reach significant differences compared to the intact group, even on the 56th day of the experiment. Thus, this indicator underwent smaller changes compared to other fractions, which is explained by the significantly lower content of highly sulfated GAGs in the structures of the cartilage matrix compared to ChS and indicates a moderate degree of severity of experimental joint damage.

Table 4

Metabolism indicators of endogenous N-acetylglucosamine in rats with experimental osteoarthritis under the influence of raleukin and glucosamine hydrochloride, (*M*±*m*)

Groups of animals	Endogenous N-acetylglucosamine content			
	Blood serum, mmol/l			Articular cartilage, mg/g
	General	Bound	Free	
Original data				
Intact control (*n*=10)	7.18±0.50	5.25±0.33	1.93±0.19	0.223±0.009
28 days				
Control pathology (*n*=10)	8.48±0.44*	6.87±0.43*	1.61±0.18	0.173±0.011*
56 days				
Control pathology (*n*=10)	8.02±0.26	6.99±0.24*	1.03±0.08*	0.148±0.013*
Raleukin 3.0 mg/kg (*n*=10)	7.76±0.49	6.10±0.40	1.66±0.11**	0.203±0.018**
Glucosamine hydrochloride 50.0 mg/kg (*n*=10)	7.61±0.68	5.89±0.52	1.72±0.15**	0.212±0.019**

*Note: statistically significant differences (p≤ 0.05): * – with a group of intact animals; ** – with the control pathology group*

Raleukin reliably reduced the total amount of GAG relative to the control pathology not only due to the reduction of chondroitin-4-sulfates, but also due to the reduction of the fraction of chondroitin-6-sulfates, the content of which reached the level of intact animals. It should be emphasised that the ratio of fractions did not change at all, and the above-mentioned changes were reliable in comparison with the group of control pathology only in terms of the dynamics of chondroitin-4-sulfates. Similar dynamics of these indicators were observed when using GA. GA and raleukin had a positive effect on the total amount and fractions of GAG in blood serum, bringing them closer to the normal level, and reducing both chondroitin-containing fractions of GAG compared to untreated animals.

Also, indicators of the exchange of endogenous N-acGA in the body of rats with experimental SSO under the influence of the researched and reference preparations were studied (Table 4). These indicators can be considered as non-specific informative markers of destructive processes of connective tissue and the effectiveness of pharmacotherapy [23–26].

The results show that in the animals of the control group on the 28th day of the experiment, a significant increase in the content of both total (by 1.2 times) and bound (by 1.3 times) fractions of N-acGA in blood serum was observed in comparison with intact rats. The level of the free form of N-acGA, although it had a tendency to decrease, was not significantly different from the indicator in the intact group. Also, a significant decrease (by 1.3 times) in the content of N-acGA in the homogenate of cartilage tissue of rats of this group was noted.

The given data testify to the destructive processes in the articular cartilage matrix and the release of destroyed remnants of biopolymers (proteoglycans, GAG, etc.) into the bloodstream, and their composition includes N-acGA. In this regard, the content of this hexosamine in the blood increases precisely due to the bound fraction, which reflects the intensity of the processes of destruction of articular cartilage.

In contrast, the level of free N-acGA reflects the intensity of regenerative processes in the connective tissue elements of the body. The decrease in its content can be explained by capture by chondrocytes and synoviocytes with subsequent inclusion in the processes of biosynthesis of newly formed GAG. Thus, the lower the content of this fraction, the less regenerative capabilities of damaged cartilage tissue.

In the course of the development of SSO, the above-described picture intensified, and on the 56th day of the study in the group of control pathology, the content of N-acGA in the tissues of the articular cartilage decreased by 1.5 times. At the same time, the content of total N-acGA in the blood serum of the control group decreased slightly and no longer had significant differences compared to the intact group. However, the level of bound N-acGA, as before, remained elevated by 1.3 times. The content of the free fraction of aminosugar decreased even more and reached the level of 1.0 mmol/l, which is 1.9 times less than in the intact group and 1.6 times less than on the 28th day of the experiment. Thus, the regenerative potential of cartilage tissue was significantly reduced.

The positive dynamics of the content of N-acGA in the blood serum of rats in all fractions was revealed in the case of use for the treatment of animals with raleukin since the obtained indicators had a tendency to normalise and were significantly different from the corresponding indicators of the control pathology group (except for the free fraction). At the same time, the level of free N-acGA increased 1.7 times compared to untreated animals, which, in turn, indicates an increase in the regenerative potential of the cartilage tissue of rats in this group. The above picture is confirmed by the results of the analysis of the content of N-acGA in the cartilage tissue, where the level of hexosamine reached 0.203 mg/g (reliably did not differ from the intact group) and significantly (by 1.4 times) exceeded the indicators of the control pathology group.

A similar situation, but somewhat more marked, was observed when using the reference drug GA. The

indicators of the content of the total and bound fractions of N-acGA in blood serum also decreased compared to the indicators of untreated animals. However, the indicators of the content of the bound fraction and N-acGA of cartilage tissue probably increased and were at the level of animals receiving raleukin. Thus, in terms of its effect on the parameters of N-acGA metabolism, raleukin is slightly inferior to the activity of GA, without statistically significant deviations, which indicates a certain effect of the drug on reducing the intensity of destructive processes in the tissues of the joints of animals with SSO and increasing the regenerative capabilities of articular cartilage.

It should be noted that the positive dynamics of endogenous N-acGA metabolism indicators, which were observed to a certain extent with the introduction of raleukin, is probably related to the peculiarities of its pharmacodynamics, in which anti-inflammatory, antioxidant, and membrane-stabilising are present, which provides a chondroprotective effect on the structure of articular tissues of rats against the background of the development of SSO.

5. Discussion of the results

As is known, changes in the production of cytokines, in particular, interleukins, play an important role in the pathogenesis of a significant number of diseases, including immune and inflammatory ones. Therefore, the use of interleukins or their antagonists for therapeutic purposes is of interest. Due to the wide spectrum of pharmacological activity, this new class of regulatory molecules has great prospects for their use as medicinal products [27], of which there are still very little on the world pharmaceutical market.

Interleukins are regulators of the substitute and inductive type of action, ensuring the launch of cascade activation of effector cells, processes of immunity, inflammation and regeneration at all stages [10].

Since IL-1, whose action is a universal response of the body to damage, is the leading place among pro-inflammatory ILs [28], a potential antagonist of IL-1 receptors can be used to treat a number of diseases, including inflammatory and degenerative diseases of connective tissue, by some of which there is arthrosis (osteoarthritis).

Therefore, the further development and introduction of drugs based on ILs and their antagonists is one of the promising directions of the development of pharmacology and medicine. All of the above substantiates the relevance of the experimental study of chondroprotective and anti-inflammatory properties of the original recombinant ARIL-1 – raleukin, which led us to plan and conduct this study.

In the course of our research, for the first time, the presence of a chondroprotective effect in ARIL-1 (raleukin) was proven, and its previously established [29] anti-inflammatory effect was studied in depth. This is especially considering the fact that the latest existing anti-inflammatory drugs do not have a chondroprotective effect or, on the contrary, have a chondrotoxic effect [30]. Therefore, the combination of anti-inflammatory and chondroprotective effects with raleukin has important clinical significance.

These studies conducted by us also confirm the data of the scientific literature regarding the presence of anti-inflammatory properties in ARIL-1 [29], which have already found clinical application in the treatment of various forms of rheumatoid arthritis with the drug Anakinra [6] – an analogue of the raleukin studied by us. However, no data on the chondroprotective properties of ARIL-1 were found in the scientific sources available to us, so the main focus of our work and its difference from previous studies was the study of the chondroprotective properties of Raleukin.

Limitations of the study. However, despite the originality of our study, it should be noted that it was conducted only on clinical and biochemical markers and does not contain histological data.

Prospects of the study. Besides, it would probably be appropriate to investigate the chondroprotective effect of raleukin not only in one model of connective tissue lesions and not only in one mode of administration of the investigated remedy.

Such shortcomings and limitations of the study are a prerequisite for our further research in the field of in-depth study of the chondroprotective properties of raleukin and the expansion of its pharmacodynamics.

6. Conclusions

According to modern manifestations, the activation of the cytokine system is one of the starting and then supporting mechanisms of the inflammatory process. This justifies the well-being and interest in the study of anti-cytokine agents – blockers of interleukin receptors – as agents for the treatment of inflammatory, in particular, rheumatological diseases.

In the model of systemic steroid osteoarthritis, raleukin contributed to the improvement of functional indicators of the condition of animals and the normalisation of their body weight; namely, it moderately reduced the content of all markers of connective tissue metabolism in the blood serum of animals, especially chondroitin sulfates and sialic acids, which can be explained by the systemic nature of its effect. In terms of its effect on the level of the main metabolites of connective tissue in the blood serum of rats, raleukin prevailed over glucosamine hydrochloride. Raleukin also contributed to a significant decrease in the total amount of glycosaminoglycans relative to control pathology, not only due to the reduction of chondroitin-4-sulfates but also due to the reduction of the fraction of chondroitin-6-sulfates, the content of which reached the level of intact animals. Raleukin had a positive effect on the total amount and fractions of glycosaminoglycans in blood serum and slowed down the development of inflammatory and destructive processes in cartilage tissue at the level of the reference chondroprotector glucosamine hydrochloride. Thus, the analysis of biochemical data against the background of experimental osteoarthritis allows us to

draw a conclusion about the high chondroprotective and anti-inflammatory potential of the recombinant IL-1 receptor antagonist.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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Data availability

Data will be made available on reasonable request.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

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