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Sensitivity To Glucocorticoids In Synovial Fluid In Rheumatoid Arthritis: The Key To Effective Therapy

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Abstract: The aim of the study was to study the nature of GCR in the synovial fluid (SF) in rheumatoid arthritis (RA).

Materials and methods. SF sampling was performed under aseptic con-ditions by puncture of the knee joint in 31 patients with RA. SF was studied immu- nopharmacologically for sensitivity to six systemic glucocorticoids – betamethasone, dexamethasone, triamcinolone, methylprednisolone, predni-sone, and hydrocortisone using an original proprietary technique.

Results. The largest number of very highly sensitive drugs are hydrocor-tisone and triamcinolone, followed by betamethasone, followed by dexame-thasone and methylprednisolone, and prednisone. Among the highly sensitive drugs, betamethasone and triamcinolone came first, hydrocortisone came sec-ond, and prednisone and dexamethasone came last. Prednisone and dexame-thasone account for the largest number of low-sensitivity patients, followed by the same distribution of betamethasone, methylprednisolone, and triamcino-lone. Among the very low-sensitivity cases, methylprednisolone account for the largest number of cases, followed by prednisone and dexamethasone, fol-lowed by triamcinolone and betamethasone. It should be noted that different degrees of sensitivity to drugs were detected in the same patient in SF.

Conclusion. The data obtained should be taken into account when ad-ministering GK intra-articularly in patients with synovitis, especially recurrent synovitis in patients with RA.

Keywords: Rheumatoid arthritis, synovial fluid, glucocorticoid sensitivity, betamethasone, dexamethasone, triamcinolone, methylprednisolone, prednisone, hydrocorti-sone.

Introduction: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation of the joints, leading to their deformation and loss of function. Despi te all the achievements of modern medicine, one of the essential methods of treatment for RA accompanied by synovitis is intra-articular administration of glucocorticoids (GK), which are able to quickly relieve symptoms in the af-fected joint [23,25]. However, despite their effectiveness, some patients show insufficient response to GK therapy or develop resistance accompanied by re-current synovitis. Understanding the mechanisms underlying this resistance, especially at the level of synovial fluid (SF), a key tissue affected by RA, is of great importance for optimizing treatment [17,22].

The fat surrounding the articular surfaces plays an important role in maintain joint health. In RA, it becomes the arena of an active inflammatory process, where immune cells, inflammatory mediators, and other biologically active substances circulate. It is in the

SF that GK interacts with target cells such as synoviocytes and immune cells, which determines their anti-inflammatory effect [33,34].

GCS act through the activation of intracellular glucocorticoid receptors (GCR). The binding of GK to GCR leads to the formation of a complex, which then moves into the cell nucleus and affects gene expression. The main mecha-nisms of the anti-inflammatory effect of GK include: suppression of pro-inflammatory gene expression, induction of anti-inflammatory gene expres-sion, direct effect on immune cells: GK can cause apoptosis (programmed death) of activated T-lymphocytes and other immune cells, as well as suppress their proliferation and function [20,21].

The sensitivity to GCR in SF in RA is determined by a complex of fac-tors, including the expression and function of glucocorticoid receptors (GCR), the amount and activity of GCR in SF synoviocytes and immune cells are criti-cal for the response to GK. the activity of enzymes metabolizing GK, interac-tion with other signaling pathways, the state of inflammation, and genetic fac-tors [33,34]. However, in many cases, resistance to GK is revealed, which is accompanied by the development of recurrent synovitis despite repeated ad-ministration of GK. GK resistance in RA can manifest itself at different levels: pre-receptor, receptor, post-receptor, and cellular [4].

Currently, there are several approaches to assessing sensitivity to GK in the SF, which can be divided into direct and indirect.

1. Direct methods: assessment of the cellular response to GK in vitro. These

methods are aimed at studying the reaction of synovial fluid cells (mainly syn-oviocytes and immune cells) to the effects of GK in laboratory conditions. As-sessment of inhibition of cell proliferation: GK has a cytostatic effect, sup-pressing the proliferation of inflammatory cells. The study may include cultiva-tion of synovial fluid cells in the presence of various concentrations of GK and assessment of their proliferative activity using such methods as: MTT test (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide)- evaluates the metabolic activity of cells, which correlates with their number [10, 25].

Immunohistochemistry with proliferation markers makes it possible to visualize and quantify cells in the division phase. The induction of apoptosis (programmed cell death in response to GK) can be assessed using: flow cytom-etry using dyes, Western blotting to determine the expression of proteins in-volved in apoptosis, and the inhibition of cytokine production [24,26]. The expression of glucocorticoid receptors (GR) can be assessed using flow cytom-etry, Western blotting, or immunohistochemistry [31].

2. Indirect methods: assessment of molecular and biochemical markers. These methods focus on the analysis of biomarkers in synovial fluid, which can re-flect a local response to GK or predict its effectiveness by analyzing the profile of cytokines and chemokines, assessing the level of matrix metalloproteinases (MMPs), and analyzing metabolomics [30].

A significant disadvantage of all of the above methods is their complexi-ty, the need for a large number of specialists, the need for complex and expen-sive equipment and reagents, attachment to a single GK (usually prednisone or dexamethasone), lack of sensitivity gradation, which makes their interpretation difficult, as well as the considerable time required to perform the study, which takes up to 10-12 days in immunohistochemical studies [16, 27]. Therefore, these studies have not found application in clinical practice, and the use of GK for intra-articular injection is carried out empirically, using data from various manuals, many of which were written many years ago. In this regard, it is rele-vant to develop simpler methods for determining sensitivity to GK in the SF in order to optimize the treatment of synovitis in RA.

Since the 80s of the last century, the phenomenon of cortisol-resistant lymphocytes has been known, i.e. such lymphocytes that do not respond to cortisol (hydrocortisone) and at the same time there is no clinical response, which was noted in the treatment of bronchial asthma. Based on these data, we developed a method for determining sensitivity to six systemic GK, since lym-phocyte isolation is a routine procedure.

The purpose of the study was to study the nature of GK in the SF in RA.

METHODS

SF sampling was performed under aseptic con-ditions by puncture of the knee joint in 31 patients with RA. The diagnosis of RA was established on the basis of medical history, physical and clinical la-boratory examination according to the criteria of the American Rheumatologi-cal Association (ARA) in 1987. All patients had II – III degree of disease activ-ity (ESR - 37.85 ± 1.15 mm/hour, CRP from 18 to 30 mg/l). The average age was 44.83±2.54 years, the average duration of the disease was 5.34±0.99 years, the average duration of joint loss was 7.1±0.2 days, and those with grade II-III disease activity (ESR-39.6±3.35 mm/h, CRP-21.8±2.43 mg/l). The average radiological stage is -2.22±0.12.

SF was studied clinically, immunologically, and immunopharmacologi-cally. The indication for an

immunopharmacological study was recurrent syn-ovitis and insufficient effectiveness of previous treatment, including previous intraarticular administration of GK (betaspan (betamethasone), kenalog, hy-drocortisone, dexamethasone).

In the aseptic conditions of the manipulation room, a puncture of the joint (most often the knee joint) is performed with a disposable dry 20-gram syringe, followed by evacuation of all available synovial fluid. The obtained SF in a volume of 0.5 - 1 ml is placed in a sterile heparinized centrifuge tube. After centrifugation for 15 minutes at 1500 rpm, lymphocytes are isolated using the Boum method at 76% ficollet and the number of lymphocytes in the Goryaev chamber is counted under a microscope at magnification. 250 (approx.5, vol-ume 50). Then, 500 ml of synovial fluid is added to individual test tubes using a measuring pipette. 100 ml of solutions of betamethasone, dexamethasone, triamcinolone (kenalog), methylprednisolone (solumedrol, urbazone), predni-sone, and hydrocortisone are added to each tube using separate measuring pi-pettes. Taking into account the bioequivalence of glucocorticoids, standard ampoules glucocorticoid solutions are diluted: dexamethasone (1 ml) is diluted with a physiological solution in the amount of 26.6 ml of sterile physiological solution (0.9% sodium chloride solution), triamcinolone (kenalog), urbazone (solumedrol, methylprednisolone) in 4 ml of sterile physiological solution, prednisone in 5 ml, and betamethasone in 22 ml of solution, respectively. Working solutions of glucocorticoids are stable for a month when stored in sterile conditions. in the dark in the refrigerator at a temperature of 8c. The re-sulting mixture is incubated in a thermostat at 37 °C for 1 hour, then stained with trypan blue and fixed with glutaraldehyde, after which the remaining lymphocytes are counted in the Goryaev chamber under a microscope. If the number of lymphocytes decreased by 1-20%, then the sensitivity result is esti-mated as very low sensitivity, 21-40% low sensitivity, 41-60% sensitive, 61-80% highly sensitive, over 80% very highly sensitive. The total duration of de-termination of sensitivity to six GK is approximately 1.5 hours [1].

RESULTS AND DISCUSSION

The table shows the distribution of sensitivity in SF in patients with RA to GK.

Table

The nature of the distribution of sensitivity to GK in the SF in patients with RA.

Medication	betame thasone	methyl predni solone	dexa metha sone	predni sone	triam cinolone	hydro cortisone
very highly sensitive	18 *(58%)*	14 *(45%)*	11 *(35%)*	11 *(35%)*	23 *(74%)*	23 *(74%)*
highly sensitive	6 *(19%)*	1 *(3%)*	3 *(10%)*	3 *(10%)*	4 *(13%)*	4 *(13%)*
sensitive	-	1 *(3%)*	1 *(3%)*	-	1 *(3%)*	-
low sensitivity	3 *(10%)*	3 *(10%)*	6 *(19%)*	8 *(26%)*	3 *(10%)*	-
very low sensitivity	4 *(13%)*	12 *(39%)*	10 *(33%)*	9 *(29%)*	-	4 *(13%)*

Note: The percentage figures are shown in parentheses.

It should be noted that the same patient had a different degree of sensi-tivity to drugs in his SF. Using our technique, for the first time, data were ob-tained on the nature of sensitivity to GK in the SF in RA.

Differences in the nature of sensitivity to GK in the SF are due, on the one hand, to the chemical structure, and, on the other, to the degree of influ-ence on the inflamed synovial membrane. When administered intra-articularly, betamethasone, triamcinolone, and hydrocortisone have a greater anti-inflammatory effect on the synovial membrane than the other GK. This, it seems to us, is due to the difference in the distribution of sensitivity of very highly sensitive patients to GK, which is important practically in the case of recurrent synovitis in RA.

Currently, the nature of sensitivity to a specific GK in the SF in RA is unknown [21]. It is known that the synovial membrane is a semi-impermeable membrane, and therefore the properties of cells produced by the synovial membrane may differ significantly from those

of similar peripheral blood cells. The mechanisms of development of this condition are very complex and have not been fully studied. It should be noted that lymphocytes in SF are produced by SF cells and their receptors differ in sensitivity. The data obtained make it possible to use the data obtained, carrying out, if necessary, the determination of sensitivity to GK in the SF, which makes it possible to more effectively stop the symptoms of synovitis by intra-articular administration of GK with the maximum degree of sensitivity [7, 33, 34].

Sensitivity to any GK in the SF means the ability of cells and molecular mechanisms in the affected joint to respond adequately to the action of the drug. This sensitivity may be reduced or changed in patients with RA, which explains the ineffectiveness of therapy in some of them.

There are a number of factors that affect sensitivity to GK:

1. Genetic factors: polymorphisms of genes encoding glucocorticoid receptors or enzymes involved in GK metabolism may affect the effectiveness of therapy [14,19].

2. Condition of the synovial membrane: chronic inflammation and fibrosis of the synovial membrane can alter its permeability and the ability of cells to re-spond to therapy [17].

3. The level of inflammatory mediators: high concentrations of certain cyto-kines or other inflammatory molecules in the synovial fluid can "overload" GK signaling pathways, reducing their effectiveness [26,30].

4. The state of glucocorticoid receptors: changes in the expression or function of glucocorticoid receptors in synovial membrane cells can lead to hydrocorti-sone resistance [9].

5. Concomitant diseases and medications: some other diseases (diabetes melli-tus) or medications taken may interact with the metabolism or the action of GK.

Betamethasone, being a synthetic glucocorticosteroid, acts by binding to intracellular glucocorticoid receptors. This complex then penetrates into the cell nucleus and modulates the expression of genes responsible for inflammato-ry processes. Betamethasone reduces the permeability of synovial capillaries, thereby reducing edema and infiltration by inflammatory cells. Sensitivity to betamethasone can be influenced by various factors: binding to proteins of the synovial fluid and permeability of the synovial membrane. The synovial mem-brane surrounding the joint acts as a barrier. Its permeability may change with inflammation, affecting the penetration of betamethasone from the bloodstream into the synovial cavity with systemic administration. With intra-articular ad-ministration, this factor is less significant, but it can still play a role in the dis-tribution of the drug [8,13].

Triamcinolone acts by binding to GCR, which are located inside cells. A decrease in GCR expression or their functional activity may lead to a decrease in sensitivity to the drug. A high degree of inflammation in the joint can affect the permeability of cell membranes and the activity of intracellular signaling pathways, which, in turn, can alter sensitivity to triamcinolone. The condition of the synovial membrane - chronic inflammation can lead to structural chang-es in the synovial membrane, which can affect its response to intra-articular in-jection [12,15,18,32].

Hydrocortisone, like other GK, has a powerful anti-inflammatory and immunosuppressive effect. When administered intra-articularly, it penetrates the synovial membrane and cells, where it binds to glucocorticoid receptors. This leads to suppression of the production of pro-inflammatory cytokines, a decrease in the activity of immune cells (macrophages and lymphocytes), and a decrease in vascular permeability, which reduces edema and the influx of in-flammatory cells into the joint [29].

Dexamethasone, like other GK, acts by binding to intracellular GK re-ceptors. This complex then penetrates into the cell nucleus and affects the ex-pression of genes regulating the inflammatory process. When administered in-traarticularly, dexamethasone suppresses the production of proinflammatory cytokines, inhibits the activity of enzymes that destroy cartilage, reduces the proliferation of synovial fibroblasts, and reduces the migration and activation of immune cells (neutrophils and lymphocytes) [5,6,11].

Prednisone, when administered intraarticularly, acts by binding to gluco-corticoid receptors (GR) inside cells. After binding, the prednisolone-GR com-plex moves to the cell nucleus, where it regulates the expression of genes in-volved in the inflammatory process. In the context of RA, prednisone tends to suppress the activity of synovial fibroblasts, macrophages, T-lymphocytes, and other cells producing pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) and enzymes that destroy cartilage [7,16,29].

Methylprednisolone, like other glucocorticosteroids, has a powerful anti-inflammatory and immunosuppressive effect. It penetrates into the cells of the synovial membrane and binds to GCR. This complex of GR-methylprednisolone then moves to the cell nucleus, where it regulates the ex-pression of genes involved in the inflammatory process. As a result, the

pro-duction of pro-inflammatory cytokines decreases, the proliferation of synovio-cytes decreases, and the activity of immune cells is suppressed [2,3, 28].

The results obtained show a clear correlation with clinical data, illustrat-ed by an example.

An example of the effectiveness of this technique. B-naya O.Sh. born in 1969: rheuma-toid arthritis, seropositive articular form, polyarthritis, Grade II. act slowly progressing course, FI II-III, R II hormone-dependent. She complained of joint pain, swelling of the knee joints, a con-stant feeling of stiffness in the joints, and dependence on hormone intake. In the anamnesis: he has been ill for 9 years, constantly takes prednisone at a daily dose of 15 mg / day, recurrent syn-ovitis has been repeatedly noted. Previously, she has repeatedly received intra-articular betaspan (sertaspan), but the effect of GK administration was 1.5-2 months. About: the condition is of moderate severity. The skin covers are several cyanotic. Increased nutrition. There is joint de-formity with partial contractures and ankyloses, pronounced swelling of the knee joints. There is no swelling. Vesicular respiration. respiratory rate 16/min. Cor: the tones are somewhat muted, rhythmic. Blood pressure is 120/80 mmHg, pulse is 80/min. The abdomen is soft, painless, easy to breathe. The liver is +0.5 cm, the edge is soft and painless. The spleen is not palpable. The large intestine is painless. The chair is adequate. Genitourinary system: a symptom of "pounding" (-) on both sides, the kidneys are not palpable. The cut is adequate. Given the presence of recurrent synovitis, a study of synovial fluid was performed for sensitivity to GK: betamethasone - very low sensitivity, methylprednisolone - very low sensitivity, dexamethasone - very highly sensitive, prednisone– very low sensitivity, triamcinolone - very highly sensitive, hydrocortisone - very low sensitivity, methotrexate - very low sensitivity. Taking into account the sensitivity results, the pa-tient was given intra-articular kenalog 40 (triamcinolone) intra-articularly, after which the recur-rence of synovia stopped.

Understanding the mechanisms of GK resistance at the level of synovial fluid is of great clinical importance:

1.Personalization of therapy: identification of patients with a predisposition to GK resistance will allow for more accurate selection of therapy. This may in-clude choosing alternative anti-inflammatory drugs or combinations that will be more effective for this group of patients.

2. Development of new therapeutic strategies: the study of molecular targets responsible for GK resistance may lead to the development of new drugs aimed at overcoming this resistance.

3.Monitoring the effectiveness of treatment can help in monitoring the re-sponse to therapy and timely correction of treatment if it is ineffective/

4. Predicting the outcome of the disease: the level of resistance to GK may be associated with a more aggressive course of RA and a worse prognosis. Study-ing these relationships will help to better predict the development of the dis-ease and plan long-term patient management.

CONCLUSION

The study of sensitivity to glucocorticoids in synovial fluid in rheuma-toid arthritis is not just an academic interest, but an urgent need to improve the quality of life of patients. The transition to personalized medicine based on a deep understanding of molecular mechanisms will allow us to fight inflamma-tion more effectively, slow down the progression of the disease and preserve joint function, providing each patient with the most appropriate and effective treatment. Further research in this area promises to revolutionize the approach to rheumatoid arthritis therapy, making it more accurate, targeted, and ulti-mately more successful.

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Contribution of the authors:

Suyarov A.A.-the general idea;

Kireev V.V. – writing an article;

Khatamov H.M. – patient selection, scientific rehabilitation.

REFERENCE

1. Aripova T.U., Kireev V.V., Suyarov A.A., Khatamov H.M., Usmanbekova H.T. A method for determining sensitivity to glucocorticoids in vitro. Utility Model Patent UMP (FAP) 2022 0219 Official Bulletin Tashkent 2023 -1(262). p.103

2. Barton KI, Chung M, Frank CB, Shrive NG, Hart DA. Methylprednisolone acetate mitigates IL1β induced changes in matrix metalloproteinase gene expression in skeletally immature ovine explant knee tissues. Inflamm Res. 2021 Jan;70(1):99-107. doi: 10.1007/s00011-020-01421-2. Epub 2020 Nov 23. PMID: 33226449.

3. Barton KI, Heard BJ, Chung M, Sevick JL, Martin CR, Achari Y, Frank CB, Shrive NG, Hart DA. Location and gene-specific effects of methylpred-nisolone

acetate on mitigating IL1β-induced inflammation in mature ovine explant knee tissue. Inflamm Res. 2017 Mar;66(3):239-248. doi: 10.1007/s00011-016-1009-z. Epub 2016 Nov 16. PMID: 27853846.

4. Burnsides C., Corry J., Alexander J., Balint C., Cosmarl D., Phillips G., Webster Marketon J. I. Ex vivo stimulation of whole blood as a means to determine glucocorticoid sensitivity. // J. Inflamm. Res. 2012;5:89-97. doi: 10.2147/ JIR.S33569. Epub 2012 Aug 22

5. Dankers W, González-Leal C, Davelaar N, Asmawidjaja PS, Mus AMC, Hazes JMW, Colin EM, Lubberts E. 1,25(OH)2D3 and dexamethasone additively suppress synovial fibroblast activation by CCR6+ T helper memory cells and enhance the effect of tumor necrosis factor alpha blockade. // Ar-thritis Res Ther. 2018 Sep 20;20(1):212. doi: 10.1186/s13075-018-1706-9. PMID: 30236152; PMCID: PMC6148958.

6. De A, Blotta H.M, Mamoni R.L, Louzada P, Bertolo M.B, Foss N.T, Moreira A.C, Castro M. Effects of dexamethasone on lymphocyte prolifera-tion and cytokine production in rheumatoid arthritis //J. Rheumatol. 2002 Jan;29(1):46-51

7. De Rijk R, Sternberg E.M. Corticosteroid resistance and disease. //Ann Med. 1997 Vol 29(1)-P.79-82.

8. Gertel S, Polachek A, Furer V, Paran D, Tzemach R, Levartovsky D, et al. Synovial monocytes from psoriatic and rheumatoid arthritis patients are modulated differently by TNF inhibitors and glucocorticoids: an ex-vivo study. // Clin Exp Rheumatol. 2023 Sep;41(9):1847-1855. doi: 10.55563/clinexprheumatol/d3mfat. Epub 2023 Mar 2. PMID: 36912319.

9. Goecke A, Guerrero J. Glucocorticoid receptor beta in acute and chronic in-flammatory conditions: clinical implications //Immunobiology. 2006;211(1-2):85-96

10. Hardy R, Rabbitt EH, Filer A, Emery P, Hewison M. et al. Local and systemic glucocorticoid metabolism in inflammatory arthritis. //Ann. Rheum. Dis. 2008;67:1204–1210

11. Kovermann NJ, Basoli V, Della Bella E, Alini M, Lischer C, Schmal H, Kubosch EJ,et al. BMP2 and TGF-β Cooperate Differently during Synovial-Derived Stem-Cell Chondrogenesis in a Dexamethasone-Dependent Man-ner. // Cells. 2019 Jun 25;8(6):636. doi: 10.3390/cells8060636. PMID: 31242641; PMCID: PMC6628125.

12. Lee YK, Choi JK, Kang YJ, Kim HW, Kim SW, Park CK et al. Tri-amcinolone-carbon nanotube conjugation inhibits inflammation of human arthritis synovial fibroblasts.//J Mater Chem B. 2016 Mar 7;4(9):1660-1671. doi: 10.1039/c5tb01693b. Epub 2015 Oct 19. PMID: 32263018.

13. Li H, Feng Y, Zheng X, Jia M, Mei Z, Wang Y, Zhang Z, et al/ M2-type exosomes nanoparticles for rheumatoid arthritis therapy via macrophage re-polarization. J Control Release. 2022 Jan;341:16-30. doi: 10.1016/j.jconrel.2021.11.019. Epub 2021 Nov 16. PMID: 34793917.

14. Olnes M. J., Kotliarov Y., Biancotto A., Cheung F., Chen J. et al. CHI Consortium effects of systemically administered hydrocortisone on the hu-man immunome // Sci. Rep. 2016; 6: 23002.P.1-15

15. Park JY, Kwon S, Kim SH, Kang YJ, Khang D. Triamcinolone-Gold Nanoparticles Repolarize Synoviocytes and Macrophages in an Inflamed Synovium. // ACS Appl Mater Interfaces. 2020 Sep 2;12(35):38936-38949. doi: 10.1021/acsami.0c09842. Epub 2020 Aug 24. PMID: 32805872.

16. Parodis I, Depascale R., Doria A. When should targeted therapies be used in the treatment of lupus nephritis: Early in the disease course or in re-fractory patients? //Autoimmunity Reviews Available online 23 August 2023, 103418 P.1-6.

17. Pongratz G. Glucocorticoid therapy in rheumatoid arthritis - pro //Dtsch Med. Wochenschr.2016 Oct;141(22):1650.doi: 10.1055/s-0042-110983.

18. Porter A, Newcomb E, DiStefano S, Poplawski J, Kim J, Axe M,et al. Triamcinolone acetonide has minimal effect on short- and long-term meta-bolic activities of cartilage.//J. Orthop Res. 2024 Nov;42(11):2426-2436. doi: 10.1002/jor.25913. Epub 2024 Jun 11. PMID: 38860529; PMCID: PMC11479848

19. Qiang Guo, Yuxiang Wang, Dan Xu, Johannes Nossent, Nathan J. Pav-los, Jiake Xu. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies //Bone Res. 2018; 6: 15. doi: 10.1038/s41413-018-0016-9.P.1-14.

20. Quax.R. AM, Koper J. W, Jong P. HP de, R. van Heerebeek, Angelique E Weel, et al. In vitro glucocorticoid sensitivity is associated with clinical glucocorticoid therapy outcome in rheumatoid arthritis// Arthritis Research & Therapy 2012, 14 (4): R195 doi: 10.1186/ar4029. P.1-12.

21. Quax RA, Manenschijn L, Koper JW, Hazes JM, Lamberts SW, van Rossum EF, Feelders RA. Glucocorticoid sensitivity in health and disease. //Nat Rev Endocrinol. 2013 Nov;9(11):670-686.

22. Rodriguez J.M, Monsalves-Alvarez M, Henriquez S, Llanos MN, Tron-coso R. Glucocorticoid resistance

in chronic diseases. //Steroids. 2016 Nov; 115: 182-192

23. Ruyssen-Witrand A., Constantin A. Controversies in rheumatoid arthri-tis glucocorticoid therapy// Joint Bone Spine 2018 Jul;85(4): 417-422.doi: 10.1016 /j.jbspin.2017.12.002

24. Sevilla L. M., Jiménez-Panizo A., Alegre-Martí A., Estébanez-Perpiñá E., Caelles C., Pérez P. Glucocorticoid resistance: interference between the glu-cocorticoid receptor and the MAPK signalling pathwaysint // J. Mol Sci.2021 Sep17;22(18): 10049.doi:10. 3390/ ijms221810049 P.1-22.

25. Takanashi S., Kaneko Y., Takeuchi T. Characteristics of patients with dif-ficult-to-treat rheumatoid arthritis in clinical practice. //Rheumatology, 2021/-Vol. 60.- Issue 11, November, P.60(11):547-5256. doi.org/ 10.1093/ rheumatology/keab209

26. Tanaka Y., Hirata S., Saleem B., Emery P. Discontinuation of biologics in patients with rheumatoid arthritis //Clin. Exp. Rheumatol. 2013 Jul-Aug;31(4 Suppl 78):S22-27.

27. Toscan, C.E., Jing, D., Mayoh, C. et al. Reversal of glucocorticoid re-sistance in paediatric acute lymphoblastic leukaemia is dependent on restor-ing BIM expression. //Br. J. Cancer 122, 1769–1781 (2020). doi.org/ 10.1038 /s41416-020-0824-8

28. Trahan RA, Byron CR, Dahlgren LA, Pleasant RS, Werre SR. In vitro effects of three equimolar concentrations of methylprednisolone acetate, tri-amcinolone acetonide, and isoflupredone acetate on equine articular tissue cocultures in an inflammatory environment. Am J Vet Res. 2018 Sep;79(9):933-940. doi: 10.2460/ajvr.79.9.933. PMID: 30153056.

29. Tulbă D, Balea M, Băicuş C. Macrophage activation syndrome at the onset of glucocorticoid-resistant systemic lupus erythematosus: a case re-port //Rom. J. Intern. Med. 2018 Mar 1;56(1):67-70

30. Vazquez-Tello A., Halwani R., Hamid Q., Al-Muhsen S. Glucocorticoid receptor-beta up-regulation and steroid resistance induction by IL-17 and IL-23 cytokine stimulation in peripheral mononuclear cells. //J. Clin. Immu-nol. 2013; 33 (2): 466–78.

31. Watanabe R, Okano T, Gon T, Yoshida N, Fukumoto K, Yamada S, Hashimoto M. Difficult-to-treat rheumatoid arthritis: Current concept and unsolved problems. // Front. Med. (Lausanne). 2022 Oct 24;9: 1049875. doi: 10.3389 /fmed. 2022.1049875. P.1-7.

32. Wesdorp MA, Bastiaansen-Jenniskens YM, Capar S, Verhaar JAN, Narcisi R, Van Osch GJVM. Modulation of Inflamed Synovium Improves Migration of Mesenchymal Stromal Cells in Vitro Through Anti-Inflammatory Macrophages. Cartilage. 2022 Jan-Mar;13(1):19476035221085136. doi: 10.1177 /19476035221085136. PMID: 35306879; PMCID: PMC9137323.

33. Wesdorp M. A. Bastiaansen-Jenniskens Y. M, van Osch M. G. J.V. Modulation of inflamed synovium improves migration of mesenchymal stromal cells in vitro through anti-inflammatory macrophages //Cartilage 2022 Vol. 13, Issue 1 https://doi.org /10.1177 /19476035221085136

34. Wesdorp M. A., Bastiaansen-Jenniskens Y. M., Capar S., Verhaar J. A.N Narcisi, R., van Osch G. J.V.M. Modulation of inflamed synovium improves migration of mesenchymal stromal cells in vitro through anti-inflammatory macrophages //Cartilage January-March 2022: 1–12.