

# THE QUESTION OF HORMONE RESISTANCE IN RHEUMATOID ARTHRITIS

<sup>1</sup>V.V. Kireev, <sup>2</sup>A.A. Suyarov, <sup>3</sup>T.A. Aripova, <sup>4</sup>H.T. Usmanbekova

<sup>1,2,3,4</sup>Institute of Human Immunology and Genomics, Academy of Sciences of Uzbekistan, Tashkent, Uzbekistan

## ABSTRACT

A study was conducted on the sensitivity of peripheral blood in 62 patients with rheumatoid arthritis (RA) to glucocorticoid hormones: hydrocortisone, prednisone, methylprednisolone, dexamethasone, triamcinolone and betamethasone. Different degrees of sensitivity to different hormones were detected, and the same patient has different degrees of sensitivity to different hormones. This should be taken into account when prescribing glucocorticoids to patients with RA. Changing hormone prescribing based on sensitivity significantly improved the result of treatment.

**KEY WORDS:** rheumatoid arthritis, hormone sensitivity, hydrocortisone, prednisone, methylprednisolone, dexamethasone, triamcinolone, betamethasone.

## INTRODUCTION

Rheumatoid arthritis (RA) is one of the most widespread diseases of high medical and social importance, in the treatment of which glucocorticosteroid hormones (GCS) are widely used. Despite the emergence of basic drugs (meto-traxate, sulfasalazine, azathioprine, etc.) and the appearance from the beginning of the 21st century of genetically engineered drugs that can stop the development of the disease, corticosteroids continue to take a strong place in the treatment of RA.

However, over the past 75 years since the start of the use of corticosteroids in the treatment of RA, many facts have been accumulated that indicate about patients having hormone-insensitivity (hormone resistance), which despite all the successes in treating this disease, remains a very serious problem [1]. According to various authors, the frequency of hormone resistance can reach 30% [2], which in absolute terms represents a large number of patients, because RA prevalence is on average 1% among the world's population.

Until now, hormones have been administered empirically based on the experience of the doctor and information gathered from textbooks and manuals.

The complexity of the problem is complicated by the fact that previously created methods for determining sensitivity to GCS were limited to determining sensitivity to a single drug (usually dexamethasone), were labor-intensive, and required a large number of reagents and rather sophisticated equipment [3]. Unfortunately, in the available literature, there is no data characterizing sensitivity to various corticosteroids.

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GCS have a different effect on blood cells, and the phenomenon of cortisol resistance of lymphocytes, i.e. such lymphocytes that do not die under the action of cortisol. That is why the use of lymphocytes as markers of sensitivity to corticosteroids seems promising [4].

The aim of this work was to study the individual sensitivity of glucocorticoid drugs in patients with RA in peripheral blood.

## MATERIALS AND METHODS

62 patients with RA were examined, 60 of them were women and 2 men. The diagnosis of RA was established according to the criteria of the American Rheumatological Association (ARA) in 1987 and the working classification proposed by the Association of Rheumatologists of Russia (2003). The age of patients ranged from 17 to 72 years (average age  $52.5 \pm 0.9$  years), with a disease duration of 2 months up to 30 years (average duration  $8.67 \pm 0.62$  years). Rheumatoid factor (RF) was detected in 54 patients, and the remaining 8 patients were seronegative. Earlier, these patients received various glucocorticoids: prednisone, dexamethasone, methylprednisolone in doses of 15-20 mg daily (in terms of prednisolone), as well as methotrexate. All patients had II – III degree of disease activity (ESR indices  $-39.19 \pm 1.28$  mm / h, CRP from  $42.6 \pm 7.8$  mg/ml). All patients for 2-3 days in the clinic conducted a blood test for sensitivity to glucocorticoid

hormones. Sensitivity to hydrocortisone, prednisolone, methylprednisolone, dexamethasone, triamcinolone, betamethasone (i.e., to almost all known glucocorticoids used in rheumatology) was determined. The sensitivity to glucocorticoids was determined as follows: 4 ml of venous blood into a sterile heparinized centrifuge tube, centrifuged for 10 min at 1500 rpm, Boum lymphocytes were isolated by 76% Ficoll and the number of lymphocytes in the Goryaev chamber was counted under a microscope, then in Separate tubes are added using a measuring pipette, 500 µl of a suspension of lymphocytes and added, to each tube, using separate measuring pipettes, 100 µl of solutions of betamethasone, dexamethasone, triamcinolone and methylprednisone, prednisolone, hydrocortisone. The resulting mixture is incubated in a thermostat at a temperature of 37°C for 1 hour, then stained with trypan

blue and recorded, after which the remaining lymphocytes are counted in a Goryaev chamber under a microscope, then sensitivity to glucocorticoids is determined depending on the number of remaining lymphocytes, if lymphocytes decreased by 10-20% - the result is evaluated as low-sensitive, 20-40% medium-sensitive, 40-60% - sensitive, 60-80% highly sensitive, over 80% - absolutely sensitive. This technique was developed and patented by the authors in the Republic of Uzbekistan. Ampouled glucocorticoid solutions were used.

Statistical processing was performed using the Exel software package.

**RESULTS AND DISCUSSION**

The results are shown in the table.

**Table 1. The distribution of sensitivity to glucocorticoid drugs in patients with RA**

A drug	Betamethasone	Methylprednisolone	Dexamethasone	prednisone	Triamcinolone	Hydrocortisone
Absolutely sensitive	18 (29,03)	6 (9,68)	18 (29,03)	16 (25,81)	14(22,58)	11 (17,74)
High sensitive	12 (19,35)	15 (24,2)	19 (30,65)	12 (19,35)	16 (25,81)	11 (17,74)
Medium sensitive	2 (3,22)	4 (6,45)	8(12,9)	5 (8,06)	6(9,68)	5(8,06)
Sensitive	15 (24,2)	8 (12,9)	9 (14,52)	14 (22,58)	12 (19,35)	11 (17,74)
Insensitive	15 (24,2)	29 (46,77)	8(12,9)	15 (24,2)	14 (22,58)	24 (38,72)

\*- note: in parentheses are percentages

The data in the table show that the sensitivity to various corticosteroids is not the same. It can be seen that the largest number of insensitive patients is detected with methylprednisolone (29) and hydrocortisone (24), and the smallest number with dexamethasone (8).

The largest number of sensitive patients was to betamethasone (15), and the smallest to methylprednisolone (8).

Among the moderately sensitive patients, the least to patients was to betamethasone, and the largest to dexamethasone (8).

Among highly sensitive patients, the largest number of individuals was to dexamethasone (19), and the least to triamcinolone (11).

All the most sensitive were patients to betamethasone and dexamethasone (18 patients each), and the smallest number was to methylprednisolone (6 people). It should be noted that the degree of sensitivity to various GCS in one patient was not the same, i.e.,

there could be absolute sensitivity to dexamethasone, average to betamethasone, low sensitivity to hydrocortisone, etc.

It is interesting to note that the number of absolutely sensitive to betamethasone and dexamethasone was 3 times more than to methylprednisolone. And among those highly sensitive to dexamethasone, it was 1.72 times higher than hydrocortisone. Among moderately sensitive patients, it was 4 times to dexamethasone compared with betamethasone. Conversely, among sensitive patients it was 1.87 times higher for betamethasone compared with methylprednisolone. Among the few, it was 3.62 times higher for methylprednisolone compared to dexamethasone. This indicates a different frequency of sensitivity depending on the drug with the same degree of sensitivity.

The mechanisms of the development of hormone resistance to GCS are different. Firstly, these are defects of the chaperone protein located on the

surface of the lymphocyte, with the help of which corticosteroids penetrate the cell. And, secondly, genetic factors leading to mutations in the genes are responsible for the development of glucocorticoid resistance [5]. The authors did not find in the accessible literature information on the nature of glucocorticoid resistance simultaneously to various GCS not only in RA, but also in other diseases requiring glucocorticoid therapy.

The results showed an unequal degree of sensitivity to various GCS drugs, which must be taken into account when prescribing GCS to RA patients. Considering the nature of sensitivity in 35 patients, glucocorticoid was replaced taking into account sensitivity, which quickly led to an improvement in the clinical condition and normalization of laboratory parameters.

**CONCLUSION**

1. Patients with RA have a different degree of sensitivity to corticosteroids.
2. In the same patient, a different degree of sensitivity to different HCR is detected.
3. The frequency of differences with the same degree of sensitivity to different corticosteroids varies.

**REFERENCES**

1. A method for predicting the effectiveness of treatment with glucocorticosteroids. RF patent No. 2382364, 2008.
2. Barnes PJ, Adcock IM. Glucocorticoid resistance in inflammatory diseases. //Lancet. 2009 Vol 30;373(9678).-P.1905-17
3. Branco RG, Garcia PC, Tasker RC. Another step in understanding glucocorticoid resistance in critical illness //Pediatr Crit Care Med. 2015 Jun;16(5):489-490.
4. Chikanza IC Mechanisms of corticosteroid resistance in rheumatoid arthritis: a putative role for the corticosteroid receptor beta isoform. //Ann N Y Acad Sci. 2002 Jun; 966:39-48.
5. Chrousos G. P., Detera-Wadleigh S. D., Karl M., Syndromes of Glucocorticoid Resistance //Ann

Intern Med. 1993;119(11):1113-1124. DOI: 10.7326/0003-4819-119-11-199312010-00009

6. Chrousos GP, Loriaux DL, Brandon D, et al. Primary cortisol resistance: a familial syndrome and an animal model. // J Steroid Biochem. 1983 Jul;19(1B):567-75.
7. De A, Blotta HM, Mamoni RL, et al. Effects of dexamethasone on lymphocyte proliferation and cytokine production in rheumatoid arthritis //J Rheumatol. 2002 Jan;29(1):46-51
8. Fajardo-Hermosillo LD, Rodríguez-Navedo Y, Nadal AJ, Vilá LM. Lymphocyte sensitivity assay as a marker for glucocorticoid resistance in lupus: report of two sisters with systemic lupus erythematosus// Lupus. 2014;23(1):88-92
9. Handa R Corticosteroids in Rheumatoid Arthritis Resurrection, Revival or Rethinking ? // Medicine Update-2011. P.270-275
10. Jayme F. Cobra; Murilo R. Melo; Claudia D. C. et al. Simultaneous evaluation of in vivo glucocorticoid sensitivity and expression of glucocorticoid receptor alpha-isoform in rheumatoid arthritis patients //Arq Bras Endocrinol Metab vol.53 no.1 São Paulo Feb. 2009  
<https://doi.org/10.1590/S0004-27302009000100005>
11. Kirwan J.R. Glucocorticoid resistance in patients with rheumatoid arthritis //Scand J Rheumatol 2007;36:165–166
12. Makrygiannakis D, Shankar Revu, Neregård P, Klint E, et al. Monocytes are essential for inhibition of synovial T-cell glucocorticoid-mediated apoptosis in rheumatoid arthritis //Arthritis Res Ther. 2008; Vol. 10(6): R147
13. Quax, R.A., Koper, J.W., de Jong, P.H. et al. In vitro glucocorticoid sensitivity is associated with clinical glucocorticoid therapy outcome in rheumatoid arthritis. //Arthritis Res Ther 14, R195 (2012). <https://doi.org/10.1186/ar4029>
14. Sara De Iudicibus, Raffaella Franca, Stefano Martellosi, Alessandro Ventura, Giuliana Decorti Molecular mechanism of glucocorticoid resistance in inflammatory bowel disease //World J Gastroenterol. Mar 7, 2011; 17(9): 1095-1108 doi: 10.3748/wjg.v17.i9.1095