Modern American Journal of Medical and Health Sciences
ISSN (E): 3067-803X
Volume 01, Issue 09, December, 2025
Website: usajournals.org

ON THE QUESTION OF RESTORATION OF SENSITIVITY TO GLUCO-CORTICOIDS WITH OMALIZUMAB IN BRONCHIAL ASTHMA

Suvarov A. A.
Khatamov K. M.
Kireev V. V.
Ochilov S. I.*
Institute of Immunology and Human Genomics,
of the Academy of Sciences of the Republic of Uzbekistan
Tashkent State Medical University*

Abstract

Objective of the study: to investigate the effect of omalizumab on the sensitivity to glucocorticoids in asthma.

Materials and methods: 15 patients with asthma at stages III and IV were examined. The determination of sensitivity to glucocorticoids was carried out using a patented original method for assessing sensitivity to glucocorticoids (hydrocortisone, prednisolone, methylprednisolone, dexamethasone, triamcinolone, betamethasone). The principle of the method is based on the sensitivity of lymphocytes to glucocorticoids. If the number of lymphocytes after incubation with glucocorticoid solutions decreased by 1-20%, the sensitivity result is assessed as very low sensitive; 21-40% - low sensitive; 41-60% - sensitive; 61-80% - highly sensitive; over 80% - very highly sensitive. All patients underwent assessment of glucocorticoid sensitivity in peripheral blood before and after 4 weeks.

Results and conclusions: 1. Against the background of omalizumab treatment, there is an increase in the degree of very high sensitivity to betamethasone by 1.18 times, to prednisolone by 1.37 times, and to hydrocortisone by 2.6 times. 2. A decrease in very high sensitivity to methylprednisolone by 1.8 times, to dexamethasone by 1.2 times, and to triamcinolone by 1.08 times is observed.

Modern American Journal of Medical and Health Sciences
ISSN (E): 3067-803X
Volume 01, Issue 09, December, 2025
Website: usajournals.org

Keywords: omalizumab, sensitivity to glucocorticoids, bronchial asthma, prednisolone, dexamethasone, hydrocortisone, methylprednisolone, betamethasone.

Introduction

Glucocorticoid drugs are widely used in various fields of medicine; however, over 70 years of their use have accumulated enough facts indicating the presence of resistance to them. The frequency of resistance varies, and in many cases, it is unknown. According to several authors, the frequency of resistance to glucocorticoids (GC) in bronchial asthma (BA) reaches 30%. However, the frequency of resistance to a specific drug remains unknown. The situation is aggravated by the fact that until recently, there were no reliable methods for determining sensitivity to glucocorticoids. The methods developed since the early 1980s to present have proven to be labor-intensive, requiring a large number of reagents and complex laboratory equipment, lacking a degree of sensitivity/resistance gradation, and are tied only to one GC, most often dexamethasone (prednisone), and also associated with one disease. Another important problem in modern medicine is the issue of overcoming resistance to GC. The question of restoring sensitivity to GCs (or increasing sensitization) is relevant, as the incidence of secondary glucocorticoid resistance increases annually. A breakthrough technology in the treatment of ARI in the last 20 years of this century has been the creation of biological gene-engineered drugs (GIDs) (biosimilars), whose use, especially in the early stages, has allowed the progression of the disease to be halted and in many cases to achieve long-term remission. This allows the prescription of GCs and immunosuppressants at minimal doses, helping to avoid the development of complications from GC therapy and immunosuppressants, and improving the quality of life for this category of patients. However, the mechanism of action of GIDs is not fully studied, and even less understood is the mechanism of restoring sensitivity to GCs. It has been established that viruses or their fragments can cause blockade of glucocorticoid sensitivity receptors, thereby reducing sensitivity to GCs and

Modern American Journal of Medical and Health Sciences
ISSN (E): 3067-803X
Volume 01, Issue 09, December, 2025
Website: usajournals.org

immunosuppressants. However, attempts to use antiviral drugs have not yielded results in restoring sensitivity.

Currently, experimental studies are being conducted using the antibacterial peptide LL-37, which allows overcoming the mechanism of disrupted sensitivity to GCs through an RNA mechanism. This drug has been used in a clinical study involving patients with glucocorticoid-resistant BA, yielding promising results. It has also been established in experiments that the mouse ortholog mCRAMP LL-37 restores sensitivity to glucocorticoids in mice suffering from asthma. In the future, the application of this substance in the treatment of lung diseases may be possible. In transplantology, through high-throughput screening, a substance 2-((4,5-dihydro-1H-imidazol-2-yl) thio)-N-isopropyl-N-phenylacetamide (GCS-3) has also been identified, which has sensitizing properties regarding dexamethasone, proving promising in the experimental treatment of acute lymphoblastic leukemia in children during bone marrow transplantation.

In in vivo experiments on mouse models of BA, it has been shown that aclidinium bromide, a long-acting muscarinic antagonist (LAMA) bronchodilator for COPD, inhibits the activity of PI3Kδ by blocking muscarinic receptors M, thereby enhancing the mediated activity of topical GCS fluticasone propionate. It has also been found that rapamycin, a macrolide immunosuppressant, increases sensitivity to dexamethasone in monocyte-macrophage cells isolated from patients with COPD. In another experimental study, it was established that the experimental drug roflumilast restores the sensitivity of blood cells from patients to dexamethasone in COPD, increasing the sensitivity of the receptors, as confirmed by western blot analysis.

It should be noted that adsorption therapy with low-density lipoproteins can restore sensitivity to immunosuppressive drugs, including corticosteroids, due to its inhibitory effect on the expression of the MDR-1 gene. However, this data has limited application and requires further study. Currently, all these data are still experimental and have been conducted not in clinical settings but on models or ex vivo; the confirmation of efficacy was performed using complex and labor-intensive methods and was also related to the use of a single drug (dexamethasone

Modern American Journal of Medical and Health Sciences
ISSN (E): 3067-803X
Volume 01, Issue 09, December, 2025
Website: usajournals.org

or prednisone). At present, the study of the effects of biologics used in the treatment of asthma, particularly omalizumab, is of interest.

Objective of the study:
To investigate the effect of omalizumab on the nature of sensitivity to glucocorticoids in asthma.

Materials and methods:
15 patients with asthma of III and IV stages of the disease were examined. The average age was 24.21±5.15 years, and the average duration of the disease was 8.16±3.26 years. The diagnosis of asthma was made according to the GINA classification (2019). Previously, patients received treatment that included bronchodilators, systemic glucocorticoids, inhalers (both with sympathomimetics and ICS), mucolytics, and antibiotics. All patients experienced exacerbations of the disease. Omalizumab (Xolair) at a dose of 150 mg (Novartis, Norway) was administered subcutaneously after a complete clinical-immunological examination. All patients underwent determination of sensitivity to glucocorticoids in peripheral blood before and after 4 weeks.
The determination of sensitivity to glucocorticoids was carried out using an original patented technique for determining sensitivity to glucocorticoids (hydrocortisone, prednisone, methylprednisolone, dexamethasone, triamcinolone, betamethasone). 1 ml of venous blood is collected from the patient, regardless of food intake, in a sterile heparinized centrifuge tube. After centering for 10 minutes at 1500 rpm, lymphocytes are isolated using the Boum method at 76% ficollet and the number of lymphocytes in the Goryaev chamber is calculated under a microscope at a magnification of 250 (approx.5, vol.50). Then 500 ml of lymphocyte suspension is added to the tube using a measuring pipette and 100 ml of glucocorticoid solution is added using a separate measuring pipette. Taking into account the bioequivalence of glucocorticoids, standard ampouled glucocorticoid solutions are diluted: dexamethasone (1 ml) is diluted with saline solution in an amount of 26.6 ml of sterile saline solution (0.9% sodium chloride solution), triamcinolone (kenalog), urbazone (solumedrol,

Modern American Journal of Medical and Health Sciences
ISSN (E): 3067-803X
Volume 01, Issue 09, December, 2025
Website: usajournals.org

methylprednisolone) in 4 ml of sterile saline solution, prednisone, and betamethasone in 22 ml of solution, respectively. These solutions are stable for a month when stored in sterile conditions in the dark in a refrigerator at a temperature of 8C. The resulting 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 estimated as very low sensitivity, 21-40% low sensitivity, 41-60% sensitive, 61-80% highly sensitive, over 80% very highly sensitive.
Statistical processing of the obtained results was performed using the Statistica 12.0 software package.

Results and Discussion

The data obtained is shown in the table

Table The effect of omalizumab on the nature of sensitivity to glucocorticoids in asthma

Character of sen sivity / Medications	Very highly sensitive		Highly sensitive		Moderately sensitive		Low sensitivity		Very low sensitivity	
	be fore	after	be fore	after	be fore	after	be fore	after	be fore	after
Betamethasone	11	13	2	1	1	0	1	0	0	1
Methylprednisolone	9	5	2	1	1	0	2	0	1	9
Dexamethasone	12	10	0	2	1	0	1	1	1	2
Prednisolone	8	11	3	1	1	0	2	2	1	0
Triamcinolone	13	12	1	2	0	0	0	1	1	0
Hydrocortisone	5	13	2	1	0	0	1	0	6	1

The table shows that during omalizumab treatment, there was an increase in very highly sensitive betamethasone (1.18 times), prednisone (1.37 times) and hydrocortisone (2.6 times), and vice versa, a decrease in very highly sensitive methylprednisolone (1.8 times), dexamethasone (1.2 times) and triamcinolone (1.08 times). It should be noted that the degree of increase in sensitivity is inversely proportional to the duration of action and the presence of a fluorine atom, and vice versa, the degree of decrease in sensitivity, on the contrary, is

Modern American Journal of Medical and Health Sciences
ISSN (E): 3067-803X
Volume 01, Issue 09, December, 2025
Website: usajournals.org

directly proportional to the duration of action and the presence of a fluorine atom. Thus, the use of omalizumab leads to the greatest increase in sensitivity to hydrocortisone and a paradoxical decrease in sensitivity to methylprednisolone.

The mechanisms by which omalizumab can alter sensitivity to HA are multifaceted and have not been fully studied. However, there are several hypotheses based on understanding the pathogenesis of asthma and the effects of both drugs.:

Reducing the overall level of inflammation: Omalizumab, by blocking IgE, reduces the activation of mast cells and basophils, reducing the release of inflammatory mediators such as histamine, cysteinyl leukotrienes, and cytokines. This overall reduction in inflammatory load may make the respiratory tract more susceptible to the anti-inflammatory effects of GK [16].

Effect on the cellular composition of inflammation: Omalizumab can affect the expression of HA receptors on various cells of the respiratory tract, including eosinophils, T-lymphocytes and mast cells. A decrease in IgE levels can lead to a decrease in the infiltration of eosinophils, which are often associated with HA resistance. In addition, omalizumab can modulate the activity of type 2 T helper cells (Th2), which play an important role in allergic inflammation and may affect sensitivity to GK [7, 10].

Changes in the expression of glucocorticoid receptors (GR): Some studies suggest that omalizumab may affect expression or function GR in the cells of the respiratory tract. A decrease in the level of IgE and related signaling pathways can indirectly lead to an increase in the amount or improvement in the functionality of GR, which makes cells more sensitive to GK [10,17].

Synergistic effect: Omalizumab and GK may act synergistically, enhancing each other's anti-inflammatory effect. Omalizumab, by reducing the activity of the allergic component of inflammation, can create conditions under which GCS can more effectively suppress other inflammatory pathways [12].

Currently, no data have been found on the effect of omalizumab on the nature of sensitivity to GK. The change in the nature of sensitivity to HA is obviously due to the blockade of B-lymphocyte receptors, changes in the intercellular cooperation of the immune response, as well as a peculiar "reprogramming" of

Modern American Journal of Medical and Health Sciences
ISSN (E): 3067-803X
Volume 01, Issue 09, December, 2025
Website: usajournals.org

receptors responsible for sensitivity to GK on the surface of lymphocytes. This mechanism explains the fact that the administration of omalizumab significantly reduces the need for HA, which leads to the restoration of sensitivity to this category of drugs. To date, the ability of biosimillares to increase sensitivity to GK and ID in the treatment of rheumatoid arthritis and other rheumatic diseases has been established. The use of rituximab probably leads to a kind of reprogramming of the receptors responsible for sensitivity to GCS and MT on the surface of lymphocytes. A study of sensitivity to GCS in RA patients showed that in patients with a low degree of sensitivity to GCS after administration of rituximba, it was revealed that there is an improvement in the degree of sensitivity to GCS, which is probably due to a change in the structure of receptors on the surface of lymphocytes, as well as the nature of intercellular immunological interactions [13].

It is this mechanism that causes differences in immunological parameters depending on the nature of sensitivity to drugs. Using the same mechanism, the principles of restoring sensitivity to GCS and MT can be explained. Rituximab, affecting the parameters of cellular immunity and changing the nature of intercellular interactions, changes the receptors of lymphocytes, which leads to the restoration of sensitivity to GCS and MT [7,8,9,15,19]. This phenomenon was empirically noted almost 20 years ago, when, with the use of rituximab, patients with RA and other autoimmune desiases developed stable remission, requiring the use of minimal doses of GCS and MT to maintain its stable state and adequate quality of life in this category of patients [1,5,8,14].

Currently, a peculiar restorative effect of tocilizumab against GCS, as well as adalimumab, has already been described. There is an interesting paper on the effect of genetically engineered drugs on the course and survival of RA, which shows that the use of rituximab significantly improves the course and survival of RA compared with TNF inhibitors and the combined use of basic immunosuppressants and, if necessary, small doses of GCS. The direct modifying effect of omalizumab on the course of asthma has been established and the anti-inflammatory effect of the drug has been proven. Omalizumab reduces eosinophilic infiltration of the submucosal layer of the bronchi in patients with

Modern American Journal of Medical and Health Sciences
ISSN (E): 3067-803X
Volume 01, Issue 09, December, 2025
Website: usajournals.org

allergic asthma, eosinophilia in sputum, which correlates with a decrease in the fraction of exhaled nitric oxide against the background of biological therapy and significantly reduces the need for GCS, both systemic and in the form of inhalers. Omalizumab reduces the thickness of the bronchial wall and increases bronchial clearance [2,11,13].

Clinical implications and prospects: The potential effect of omalizumab on GK sensitivity has important clinical significance. In patients with insufficient sensitivity to GK receiving omalizumab, one can expect:

Improved asthma control: Reduced frequency of exacerbations, reduced daytime and nighttime symptoms, improved lung function.

The possibility of reducing the dose of GK: In some cases, if stable disease control is achieved, it may be possible to gradually reduce the dose of inhaled or systemic GCS, which will reduce the risk of side effects associated with their prolonged use.

A more predictable response to therapy: Understanding how omalizumab affects GK. A sensitivity can help physicians more accurately predict response to combination therapy and optimize treatment strategies.

The need for further research: The mechanisms underlying the effect of omalizumab on GK sensitivity require further study. Additional research is needed to better understand which patients are most likely to benefit from combination therapy and how to optimize the dosage of GK when used simultaneously with omalizumab.

Conclusions:

1. Against the background of omalizumab treatment, there is an increase in the degree of very highly sensitive to betamethasone by 1.18 times, to prednisone by 1.37 times and to hydrocortisone by 2.6 times.
2. There is a decrease in very highly sensitive to methylprednisolone by 1.8 times, to dexamethasone by 1.2 times and to triamcinolone by 1.08 times.

Modern American Journal of Medical and Health Sciences
ISSN (E): 3067-803X
Volume 01, Issue 09, December, 2025
Website: usajournals.org

References

1. Kadushkin A.G., Taganovich A.D., Kolesnikova T.S., Khodosovskaya E.V. Changes in the chemotaxis of monocytes and lymphocytes in the blood of patients with chronic obstructive pulmonary disease under the influence of budesonide and azithromycin. // Health and environmental issues. 2022;19(4):101–108. doi: 10.51523/2708- 6011.2022-19-4-14
2. Knyazheskaya N.P., Anaev E.Kh., Belevsky A.S., Kameleva A.A., Safoshkina E.V., Kirichenko N.D. Omalizumab and modification of the natural course of bronchial asthma. //Medical advice. 2021;(16):17-25. https://doi.org/10.21518/2079-701X-2021-16-17-25
3. Shaporova N. L. Mechanisms of formation and methods of correction of drug dependence and steroid resistance in patients with bronchial asthma. // Abstract. diss… Doctor of Medical Sciences, St. Petersburg, 2003, Pavlov St. Petersburg State Medical University, 32 p.
4. Shimanovsky N.L. Glucocorticoid resistance: mechanisms and clinical significance // Pharmateca 2005. - No. 7.- pp.27-32.
5. Adlowitz D.G, Barnard J, Biear JN, Cistrone C, Owen T et al. Expansion of activated peripheral blood memory B cells in rheumatoid arthritis, Impact of B cell depletion therapy, and biomarkers of response. //PLoS One. 2015 Jun 5;10(6):e0128269. doi: 10.1371/journal.pone.0128269. 19P.
6. Bergantini L, d'Alessandro M, Cameli P, Vietri L, Vagaggini C, Perrone A, Sestini P, Frediani B, Bargagli E. Effects of rituximab therapy on B cell differentiation and depletion. //Clin Rheumatol. 2020 May;39(5):1415-1421. doi: 10.1007/s10067-020-04996-7.
7. Bernstein JS, Wechsler ME. Eosinophilic respiratory disorders and the impact of biologics. //Curr Opin Pulm Med. 2023 May 1;29(3):202-208. doi: 10.1097/MCP.0000000000000951. Epub 2023 Mar
8. Chambers E.S, Nanzer A.M, Pfeffer P.E, Richards DF, Martineau A.R, Griffiths C.J, Corrigan C.J, Hawrylowicz C.M. Dendritic cell phenotype in severe asthma reflects clinical responsiveness to glucocorticoids. //Clin. Exp. Allergy. 2018 Jan;48(1):13-22. doi: 10.1111/cea.13061.

Modern American Journal of Medical and Health Sciences
ISSN (E): 3067-803X
Volume 01, Issue 09, December, 2025
Website: usajournals.org

9. Chen Y., Liu H., Yan Y., H. Chen et al. Methotrexate and electrostimulation cooperate to alleviate the relapse of psoriasiform skin inflammation by suppressing memory T cells. // Biochem. Pharmacol 2024 Jan: 219:P.115979. doi: 10.1016/j.bcp.2023.115979.
10. Chen F, Liang L, Chu FF, Lu C, Xu C. Effects of omalizumab combined with budesonide formoterol on clinical efficacy, pulmonary function, immune function, and adverse reactions in children with moderate and severe allergic asthma. // Allergol Immunopathol (Madr). 2023 Jul 1;51(4):182-188. doi: 10.15586/aei.v51i4.926. eCollection 2023.
11. Hao X., Han J., Zeng H., Wang H., Li G. et al. The effect of methylprednisolone prophylaxis on inflammatory monocyte subsets and suppressive regulatory T cells of patients undergoing cardiopulmonary bypass. // Perfusion 2019 Jul;34(5):364-374. doi: 10.1177/ 0267659118820777
12. Israel E, Reddel HK. Severe and Difficult-to-Treat Asthma in Adults. N Engl J Med. 2017 Sep 7;377(10):965-976. doi: 10.1056/NEJMra1608969.
13. Leandro M, Isenberg D.A. Rituximab- The first twenty years. //Lupus. 2021 Mar;30(3):371-377. doi: 10.1177/0961203320982668.
14. MacDonald C, Piper R. C. Puromycin and methotrexate resistance cassettes and optimized cre-recombinase expression plasmids for use in yeast. //Yeast 2015 May; 32(5): 423–438. doi: 10.1002 /yea.3069
15. Mulleman D. Do immunoglobulin levels and CD4 cell count interact during Rituximab treatment? //Arthritis Rheumatol. 2014 Jan 27. doi: 10.1002 /art.38361.2P
16. Salciccioli JD, Israel E. Asthma Biologics: Lung Function, Steroid-Dependence, and Exacerbations. // Immunol Allergy Clin North Am. 2024 Nov;44(4):693-708. doi: 10.1016/j.iac.2024.08.002. PMID: 39389718; PMCID: PMC11540338.
17. Solèr M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, Thirlwell J, Gupta N, Della Cioppa G. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. //Eur Respir J. 2001 Aug;18(2):254-61. doi: 10.1183/09031936.01.00092101. Erratum in: Eur Respir J 2001 Oct;18(4):739-40. PMID: 11529281.

Modern American Journal of Medical and Health Sciences
ISSN (E): 3067-803X
Volume 01, Issue 09, December, 2025
Website: usajournals.org

18. Sun DD, Xu TT, Zhou WF, Dai YR. Role of roxithromycin on glucocorticoid resistance of human bronchial epithelial cells and its mechanism. //Zhonghua Yi Xue Za Zhi. 2017 Jul 25;97(28):2215-2219.

19. Tavakolpour S, Alesaeidi S, Darvishi M, GhasemiAdl M, Darabi-Monadi S, et al. A comprehensive review of rituximab therapy in rheumatoid arthritis patients. //Clin. Rheumatol. 2019 Nov;38(11):2977-2994. doi: 10.1007/s10067-019-04699-8.