

THE EFFECT OF OMALIZUMAB ON CERTAIN CYTOKINES IN THE TREATMENT OF SEVERE BRONCHIAL ASTHMA

Kireev V. V. 1

Suyarov A. A. 1

Musakhodjaeva D. A.1

Yuldashev I. R. 2

Abdullaev N. Ch. 2

Ochilov S. N.1

Erkinov N. G. 1.

1 Institute of Immunology and Human Genomics of the
Academy of Sciences of the Re-public of Uzbekistan

2 Tashkent State Medical University

Abstract

The article examines the effect of anti-IgE therapy (Omalizumab) on the systemic level of key interleukins (IL 1, IL 2, IL 4, IL 6, IL 10, IL 18) in patients with severe uncontrolled asthma. The role of the drug in the modulation of Th2-dependent inflammation and restoration of immune homeostasis is analyzed.

The aim of the study was to study the effect of Omalizumab on the level of certain cytokines in severe asthma.

Materials and methods. 35 patients with severe asthma were examined. The level of cytokines in peripheral blood IL-1, IL-2, IL-4, IL-6, IL-10 and IL-18 was determined before and 2 weeks after administration of Xolar (Omalizumab) at a dose of 150 mg.

Results. When Omalizumab was administered, there was a significant increase in the levels of IL 2, IL 10, and IL 18.

Conclusions. Omalizumab therapy has a complex effect on cytokines, a new profile of patients with severe asthma.

Keywords: Bronchial asthma, Omalizumab, interleukins.

Introduction

Bronchial asthma (BA) is a heterogeneous disease characterized by chronic inflammation of the respiratory tract; it affects approximately 330 million people worldwide, with severe BA accounting for about 10–15% of the total incidence. In the pathogenesis of severe forms of BA, a key role is played by a cytokine cascade mediated by the activation of mast cells and eosinophils through IgE-dependent mechanisms. Omalizumab, a humanized monoclonal antibody to IgE, blocks the binding of free IgE to high-affinity receptors (FcεRI), which leads to a cascade change in the cytokine profile. It was the first biological drug developed for the treatment of severe asthma in 2007.





Over the years of using Omalizumab, extensive experience has been accumulated, indicating its effect on many aspects of the disease's pathogenesis. Currently, its remodeling effect on the bronchial tree, IgE levels, and certain pro-inflammatory cytokines has been established [1], [2], [3]. It has been established that the reduction in the level of Th2 cytokines under the influence of Omalizumab is dose-dependent and prolonged. The suppression of the activity of these pro-inflammatory mediators does not occur immediately but develops over the first 16–32 weeks of regular injections [4], [5]. Despite the fact that 29,800 publications have been devoted to this issue over the past 10 years (according to PubMed), the effect of Omalizumab on anti-inflammatory cytokines has not been sufficiently studied, which necessitates further investigation.

The aim of the study: to investigate the effect of Omalizumab on the levels of certain cytokines in severe asthma.

Materials and methods

Thirty-five patients with severe asthma were examined as part of an open longitudinal study. The diagnosis of asthma was established in accordance with the GINA classification (2025). The study was conducted at the Institute of Immunology and Human Genomics in Tashkent (Uzbekistan) between April 2025 and March 2026. All participants signed an informed consent form. The study was approved by the Ethics Committee of the Ministry of Health of the Republic of Uzbekistan (Protocol No. 9 dated April 3, 2025) and conducted in accordance with the principles of the Declaration of Helsinki.

The exclusion criteria were:

- presence of/previously had tuberculosis and oncological diseases of all localizations;
- patients with asthma who had not previously received glucocorticoids; patients with asthma that developed after recovering from COVID-19;
- presence of residual changes in the lungs after recovering from COVID-19. occupational asthma;
- asthma associated with medication use (NSAIDs and ACE inhibitors);
- concomitant allergic and endocrinological diseases (excluding diabetes mellitus);
- other somatic diseases in a state of pronounced decompensation;
- age under 18 years; refusal to provide informed consent.

Table 1 presents the clinical characteristics of the examined patients.



Table 1 Clinical characteristics of the examined patients (M±m)

Parameter		The number of patients (%)
male/female		16/19 (45,7/54,3)
Average age, years		30,45±3,41 (18-72 years)
The average duration of the disease, years		5,71±0,28 (2-30 years)
Smoking at the time of the study, %		12 (34,3)
BMI, kg/m ²		27,38±0,11
BA stages	4	41 (28,3)
	5	25 (17,2)
Phenotypes of asthma:	atopic	5 (14,3)
	hormone-dependent	12 (34,3)
	with a late debut (≥ 40 years)	9 (25,7)
	in combination with COPD	9 (25,7)
Eosinophils, % (in blood)		6,69±0,75
Eosinophils 10 ⁶ , abs (blood)		0,51±0,02
Frequency of attacks per month		2,9±0,12 (1-7)
The number of ambulance calls, per month.		2,31±0,14 (1-5)
The number of hospitalizations in the last 12 months.		2,8±0,2 (1-4)
Control over BA according to ACQ-5, average score		2,1±0,11 (1,6 – 4,1)
FEV1, % (after a bronchodilator test)		78,2±5,6 (54 -98)
S0 ₂ , %		93,4±0,97 (78-99)
Peak flow measurement, L/min		25,4±1,8 (7,8-36,2)

Note: *BMI is the body mass index All patients had an exacerbation of the disease.

Before starting treatment, all patients underwent routine clinical and instrumental examinations. Previously, these patients received various inhalers, various glucocorticoids, including systemic ones, bronchodilators, antihistamines, and antibiotics. However, the previous treatment was ineffective. The drug Xolar (Omalizumab) in a dose of 150 mg (Novartis, Norway) was administered subcutaneously after a complete clinical and immunological examination in the morning hours after meals.

The level of cytokines in peripheral blood IL-1b, IL-2, IL-4, IL-6, IL-10 and IL-18 was determined by ELISA according to the manufacturer's instructions (Vector-Best) before and 2 weeks after administration of Xolar (Omalizumab) at a dose of 150 mg subcutaneously. The control group consisted of 20 practically healthy individuals matched by sex and age.

Statistical processing of the obtained data was performed using R software (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria) and Novo Forecast Lite. Normality distribution was assessed using the Kolmogorov–Smirnov test. The reliability of the obtained data

was evaluated using the Student's t-test and the Mann–Whitney U-test. Values of $p < 0.05$ were considered statistically significant.

Results and discussion

The obtained results are presented in Table 2.

Table 2 The effect of omalizumab on the level of cytokines in the blood of patients with BA (M±m)

Cytokines	Before treated	After treated	Control
IL 1, pg/ml	183,68±20,63*	221,84±23,14*	27,25 ± 2,39
IL 2, pg/ml	74,64±1,60*	74,29±3,19*	11,08 ± 3,41
IL 4, pg/ml	14,38±0,5*	14,19±0,75*	3,24 ± 1,40
IL 6, pg/ml	30,04±2,04*	27,03±2,62*	5,91 ± 2,08
IL 10, pg/ml	2,79±0,01*	2,73±0,02*	6,72 ± 1,57
IL 18, pg/ml	88,9±4,32*	85,9±3,33*	64,15 ± 4,24

Note: *-significant difference between the values control group (healthy persons).

From the data in Table 2, it is evident that there is a significant increase in the level of IL-1 by approximately 5.3 times compared to the control group, with no significant difference between the groups. A significant increase in the level of IL-2 is observed — by 3.9 times before treatment and 5.5 times higher after treatment, with its level increasing by 1.41 times ($p < 0.01$). An increase in the level of IL-4 is detected — by a factor of 84.4 — compared to healthy individuals, also without a significant difference before and after treatment, with an insignificant trend towards a decrease. Similar changes occur with the level of IL-6, which turned out to be elevated by a factor of 21.72 compared to the control group, without a significant difference between the study groups, with a trend towards a decrease. A significant increase in IL-10 is observed during treatment with Omalizumab, with a 1.46-fold increase ($p < 0.01$); prior to treatment, the IL-10 level increased 14.48-fold before treatment and 21.25-fold after treatment compared to the control group. A significant increase in IL-18 is detected, with a 3.09-fold increase before treatment and a 3.63-fold increase after treatment ($p < 0.05$) compared to healthy individuals.

Figure 1 illustrates the heterogeneous effect of a single administration of Omalizumab on the cytokines IL-1, IL-4, IL-6, IL-10, and IL-18.

Discussion

In the pathogenesis of asthma, in addition to IgE-mediated allergic inflammation, pro-inflammatory cytokines such as IL-1, IL-6 and IL-4 play a key role; they are responsible for enhancing the inflammatory response and bronchial hyperreactivity. Modern studies show that by suppressing basophils and mast cells, Omalizumab mediates a reduction in the release of a wide range of inflammatory mediators. However, researchers recommend assessing the effectiveness of omalizumab after 16 weeks from the start of treatment, as it is believed that earlier assessment may fail to identify 100% of patients who will respond to Omalizumab (Holgate et al., 2009) [6].

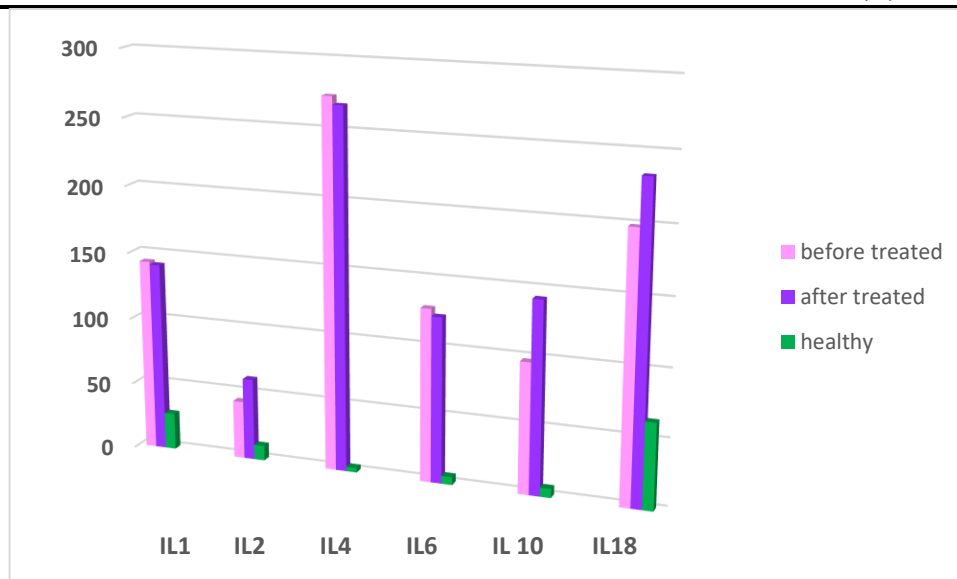


Fig. 1. Dynamics of cytokines against the background of a single administration of Omalizumab.

In our study, we assess the so-called “acute effect” of the drug on the levels of pro-inflammatory and anti-inflammatory cytokines — something that the authors have not found in the available literature. It is well known that Omalizumab therapy leads to a reduction in the overall level of pro-inflammatory cytokines, including suppression of IL-1 activity. The involvement of IL-1 in the pathogenesis of asthma is associated with the activation of epithelial cells. Omalizumab exerts an indirect inhibitory effect on IL-1 production, which contributes to a reduction in the intensity of the inflammatory response [7], [8]. Our study reveals a trend towards a decrease in IL-1, which aligns with previously obtained data from other researchers; however, according to the authors, this is due to the single administration of the drug.

IL-2, the main growth factor for T-lymphocytes, demonstrates reduced activity during Omalizumab therapy. This reduction is secondary in nature and is a consequence of reduced antigenic stimulation and the overall allergic load on the immune system, which prevents excessive proliferation of the T-cell compartment [8], [9]. The identified significant increase in IL-2, in our opinion, is due both to the assessment after a single administration of the drug and to the fact that there is a disruption in the cooperation of cytokines in the pathogenesis of asthma. Therefore, the obtained results differ from the data obtained 16 weeks after the start of treatment with Omalizumab. Also, suppression of the Th2 response with Omalizumab sometimes can lead to a compensatory increase in the activity of Th1 cells. Since IL-2 is the main cytokine produced by Th1-lymphocytes, its level may temporarily increase during the restructuring of the immune response [10].

To date, the effect of Omalizumab on Th2-associated cytokines has been well studied. IL4 is a central cytokine that determines the differentiation of type 2 T-helper cells (Th2) and stimulates the synthesis of IgE by B-lymphocytes. Omalizumab reduces the level of IL 4 in asthma. It binds free IgE antibodies in the blood and prevents them from activating immune cells. The basis of this mechanism is the disruption of the inflammatory chain, in which an allergen, upon entering the body, binds to IgE molecules on the surface of mast cells, basophils, and dendritic cells. This causes the cells to release inflammatory substances, including IL-4. Omalizumab blocks this process. This results in the



suppression of the Th2 response: IL-4 is the main regulator of allergic inflammation and is produced by type 2 T-helper cells (Th2). By blocking IgE, Omalizumab reduces the ability of immune cells to recognize allergens. As a result, the production of IL-4 itself is reduced [11].

IL-4 plays a key role in stimulating B cells to synthesize IgE and in attracting eosinophils to the respiratory tract. A decrease in IL-4 levels leads to reduced inflammation, bronchial edema, and the number of eosinophils in sputum. This effect is due to the disruption of the positive feedback loop: a decrease in the level of free IgE reduces the activation of mast cells and basophils, which in turn reduces the production of IL-4 and suppresses allergic inflammation [12]. In our study, the slight decrease in IL-4 levels is due to the determination of its values after a single administration of the drug.

Systemic inflammation in severe asthma is associated with an increase in the levels of a number of pro-inflammatory cytokines. The administration of Omalizumab causes modulation of pro-inflammatory cytokines. Currently, the key role of IL-6 in the development of inflammation in asthma has been established. As a marker of systemic inflammation, IL-6 is involved in maintaining bronchial hyperresponsiveness. Clinical data indicate a decrease in IL-6 levels during Omalizumab therapy, which correlates with a reduction in the frequency of exacerbations. IL-6 is a key pro-inflammatory cytokine whose levels are elevated in bronchial asthma. It plays a significant role in the development of inflammatory reactions in the bronchi, the intensification of airway hyperreactivity, and the formation of a severe course of the disease [13]. According to the authors, due to the single administration of Omalizumab, only a tendency towards a decrease is observed. The reduction of IL-6 does not occur instantly: it is a delayed effect that develops due to the gradual suppression of allergic inflammation (M. Roth, M. Tamm, 2010).

The effect of Omalizumab on IL-10 is interesting. The drug does not directly block IL-10. Its molecular effect lies in the profound inhibition of the IgE-mediated pathway (in particular, the activity of mast cells and basophils), which creates a favorable environment for the restoration of immune balance. Although the main focus in the study of the drug is on suppressing pro-inflammatory factors involved in the development of inflammation in asthma, researchers note its complex effect on the cytokine profile, including the key anti-inflammatory cytokine IL-10. The regulatory mechanisms of IL-10 play a critical role in immunological tolerance by suppressing the activity of pro-inflammatory cells. A number of studies have reported an increase or normalization of IL-10 levels in patients receiving Omalizumab. This indicates the restoration of the regulatory function of the immune system and a shift from a pro-inflammatory profile to an anti-inflammatory one [14], [15]. Our study reveals a significant increase in the level of IL-10, which is due to both the suppression of pro-inflammatory cytokine production and the indirect stimulation of IL-10 production to suppress an excessive immune response.

It has been established that Omalizumab does not have a direct effect on the level of IL 18. However, according to studies, a high level of IL 18 in the blood serum may serve as a prognostic marker indicating reduced efficacy of Omalizumab therapy in patients with severe asthma. It should be noted that a decrease in IL 18 is possible only with long-term use of Omalizumab over a period of 2 years; with a single administration, its increase is observed due to the suppression of pro-inflammatory cytokines [16]. The results of our study show a significant increase in the level of IL-18, which is due to a decrease in pro-inflammatory cytokines caused by the binding of free IgE to the formation of





large circulating immune complexes. As a result, the body perceives them as objects to be disposed of, which temporarily enhances macrophage activity and triggers the release of pro-inflammatory cytokines, including IL-18, before the onset of a general anti-inflammatory effect [17].

Omalizumab is capable of regulating the levels of most cytokines and chemokines in patients who respond to treatment. However, in patients who do not respond to treatment, it is unable to modulate specific pro-asthma cytokines and chemokines due to their association with the individual body mass index, which Omalizumab does not affect [18], [19], [20], [21].

Conclusion

Omalizumab therapy has a complex effect on the cytokine profile of patients with severe asthma. The mechanism of action of the drug involves not only the blockade of IgE but also systemic modulation of the immune response: a reduction in the level of pro-inflammatory cytokines (IL-4, IL-6, IL-18) and the restoration of the activity of regulatory mechanisms (IL-10). This readjustment of the cytokine status is the pathogenetic basis for the high clinical efficacy of Omalizumab in the treatment of severe asthma.

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Contribution of the authors:

Suyarov A.A. – general idea, editing

Kireev V.V. – writing a paper, statistical processing

Musakhodgaeva D.A., Yuldashev I.R., Abdullaev N.Ch. - participation in the development of the method cytokines

Ochilov S.I. Erkinov N.G – selection of patients.

All the authors made a significant contribution to the search and analysis work and the preparation of the article, read and approved the final version before publication.

Information about the authors:

Akram Amirkulovich Suyarov – Doctor of Medical Sciences, Professor, Head of the Laboratory of Allergo-and Immunopharmacology at the Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan. suyarovakram5@gmail.com. <https://orcid.org/0000-0002-2909-9820>

Vadim Vladimirovich Kireev – Doctor of Medical Sciences, Leading Researcher at the Laboratory of Allergo-and Immunopharmacology at the Institute of Human Immunology and Genetics of the Academy of Sciences of the Republic of Uzbekistan <https://orcid.org/0000-0003-1793-980X> Address for correspondence xabaas@yandex.ru

Ilkhom Ruzievich Yuldashev - Doctor of Medical Sciences, Professor, Head of the Department of Allergology, Clinical Immunology and Microbiology at Tashkent Medical University. e-mail: yuldashov.ilkhom@mail.ru

Nurboy Chunnievich Abdullayev Doctor of Medical Sciences, Associate Professor of the Department of Allergology, Clinical Immunology and Microbiology of Tashkent Medical University. e-mail: nurbay_abdullayev@mail.ru. <https://orcid.org/0000-0003-4725-5855>.

Ochilov Sardor Ilhom ugli – junior research fellow at the Laboratory of Allergo-and Immunopharmacology at the Institute of Human Immunology and Genetics of the Academy of Sciences of the Republic of Uzbekistan. sardorochilov100@gmail.com. <https://orcid.org/0009-0000-0534-808X>





Nodirbek Gayrat Ugli Erkinov is a junior researcher at the Laboratory of Allergo- and Immunopharmacology at the Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan E-mail: erkinov0205@gmail.com. <https://orcid.org/0009-0001-9667-3765>.

