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Original Article

Retrospective analysis of laboratory results in 18 cases of severe asthma treated with omalizumab

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Abstract: Objective: The aim of this study was to explore the laboratory results in severe as asthma patients with omalizumab therapy and provide evidence for estimating omalizumab efficacy. Methods: Retrospective study of 18 patients with severe asthma received omalizumab therapy in Shanghai General Hospital from 2020 to 2022 was performed. The basic data of patients were collected. The absolute number and the percentage of basophil and eosinophil in peripheral blood, total IgE level in serum, and as pulmonary function were detected at the beginning of treatment and 4 months after treatment. Differences between two groups were analyzed using Paired T test. Results: The most common allergens collected from patients with moderate to severe asthma were dust mite (positive ratio 55.56%), mixed mold (16.67%), cat and dog dander, and Aspergillus fumigatus (11.11%). There was no significant difference in eosinophil and basophil counts in peripheral blood between the two groups. However, serum total IgE levels increased from (437.55±279.35) KU/L to (1071.42±721.28) KU/L (P=0.004), and FEV1/FVC ratio increased from (65.53±14.15)% to (73.91±13.63)% (P=0.005) after 4 months of treatment. Conclusions: The existing laboratory indicators for evaluation of omalizumab efficacy are still very limited, and new biomarkers need to be further developed. Elevated serum IgE levels at four weeks of treatment and FEV1/FVC may be potential indicators for omalizumab monitoring.

Keywords: Omalizumab, asthma, serum IgE, biomarker

Introduction

Bronchial asthma is a respiratory disease with airway hyperresponsiveness, and airflow restriction caused by chronic airway inflammation [1]. The results of the 2019 Chinese Adult Lung Health Study showed that the incidence of bronchial asthma in people aged over 20 years old in China was 4.2% [2] and a significant number of patients was inadequately controlled. Moreover, asthma is often accompanied by other allergic diseases such as rhinitis [3] and atopic dermatitis [4], which increase the complexity of diseases and difficulty of clinical treatment, and the economic burden.

At present, the main therapeutic strategy for allergic asthma is based on symptomatic control, including antileukotrienes, antihistamines, hormones, and other drugs. The monoclonal antibody against IgE is the first therapeutic antibody for asthma around the world and was approved for clinical use in China since March 2018. Omalizumab has been reported to reduce the rate of severe and moderate-to-severe exacerbations and the use of glucocorticoid. Omalizumab is administered subcutaneously every 2 to 4 weeks, and effectiveness is assessed at 16 weeks based on overall asthma control. If significant improvement occurs, omalizumab treatment will be continued. However, if no significant improvement in symptoms is observed after prolonged use for 6 to 12 months, omalizumab treatment will be terminated. Clinical research results showed that the omalizumab treatment was effective in about

60-80% of the asthma patients. Until now, the method to evaluate its efficacy is still mainly based on clinical symptoms, and objective laboratory indicators are still limited.

In this study, laboratory data (including total IgE level, blood count, lung function, and FeNO detection) of patients with severe bronchial asthma treated with omalizumab in Shanghai General Hospital since 2020 was colleceted and analyzed, to explore safe and simple laboratory indicators for omalizumab treatment evaluation.

Material and methods

Subjects

18 patients with bronchial asthma who received omalizumab therapy in the respiratory department of Shanghai General Hospital from November 2020 to December 2023 were collected as retrospective study subjects. Clinical data of these cases, including age, sex, concomitant allergic diseases, white cell counts in peripheral blood, and serum allergen specific and total IgE levels.

White blood count and classification

The Mindray blood routine analyzer BC-5390 is used to achieve the classification of white blood cells by using semiconductor laser, flow cytometry technology combined with thermostatic cytochemical staining.

Total IgE in serum

The total IgE level (tIgE) was measured by Thermo Scientific™ automatic fluorescence immunoassay analyzer Phadia 250. The tIgE level > 100 KU/L represented positive and sIgE > 0.35 KUA/L was positive.

Lung functions

Pulmonary ventilation is measured in strict compliance with the protocols in pulmonary function testing guidelines [5]. The three pulmonary ventilation function indexes of forced vital capacity (FEV1), forced vital capacity (FVC) and forced vital capacity in second 1 (FEV1/FVC) were recorded in detail.

Omalizumab treatment

According to guidelines and consensus for the treatment of allergic asthma with omalizumab [3, 6], the dosage of omalizumab was calculated by patient's body weight and initial serum total IgE level, and the treatment period usually lasted for 4-12 months.

Statistical analysis

The data is analyzed using SPSS_Statistic_26.0 statistical software. Enumeration data is represented by frequency (N) and percentage (%), and normally distributed metric data is represented by mean ± standard deviation (x±s). The pairing T test was used to compare the data between the two groups before and after treatment.

Results

Clinical data for patients with asthma

Data from patients with severe bronchial asthma who received omalizumab at Shanghai General Hospital from November 2020 to December 2022 was collected. A total of 18 patients with an average age of 54±14.45 years were collected. Among them, 5 cases had allergic rhinitis and 2 cases had allergic pulmonary aspergillosis; Fifteen of them underwent allergen-specific IgE testing. The results showed that the ratio of patients allergic to dust mite was the highest, accounting for 55.56%. The proportion of patients with mixed mold allergy ranked second, accounting for 16.67%, and other allergens (cat and dog dander and Aspergillus fumigatus) allergy ranked third, accounting for 11.11%. Among the 18 cases, 16 (88.89%) had a treatment course of more than or equal to 4 months, and 3 (16.67%) had a treatment course of 10 months or more.

Comparison of total IgE in serum levels at the beginning of treatment and 4 months after treatment

Some of the patients did not perform regular blood test, and the results for total IgE levels were incomplete. In this study, full data of 10 patients before treatment and 4 months after treatment (* marked in **Table 1**) were collected, and the number and ratios of peripheral blood eosinophil and basophil counts, and serum total IgE levels were compared between the two groups. There were 3 males (30%) and 7 females (70%) among the 10 patients, with a mean age of 48±15.80 years and a baseline total IgE level of 437.55±279.35 KU/L (see **Tables 1** and **2**). Comparing the serum total IgE

Table 1. Clinical data for patients with asthma

Number	Sex	Age	With other allergic diseases	Allergen specific sIgE (KUA/L)	Dosage (mg)	Course (times)
*1	F	62	/	d1(20.40); d2(18.80); e1(62.2); e5(4.74)	450	5
*2	M	65	/	i6(0.56); e1(0.36); e5(17)	450	6
*3	F	27	Allergic rhinitis	d1(0.36)	150	5
4	M	53	Allergic bronchopulmonary aspergillosis	d1(1.31); mx2(0.89); m3(4.83); d2(1.14); i6(11.10)	600	4
Δ*5	M	45	Allergic rhinitis	d1(4.18); d2(3.70); i6(5.12); f4(1.03); f23(0.84); f24(3.31)	600	10
6	F	66	/	< 0.35	150	2
7	F	68	Allergic rhinitis	No data	600	4
8	M	61	Allergic bronchopulmonary aspergillosis	d1(55.70); mx2(7.29); m3(42.30); d2(37.90)	600	3
Δ*9	F	37	Allergic rhinitis	d1(10.60); d2(18.80); i6(0.64)	450	11
10	M	58	/	No data	450	6
*11	M	30	/	No data	450	6
12	M	70	/	< 0.35	600	6
*13	F	48	Allergic rhinitis	< 0.35	150	6
14	F	63	/	d1(1.68); d2(4.13)	150	8
Δ*15	F	72	/	d1(0.41); d2(0.54); i6(0.35)	600	12
16	M	58	/	d1(0.43); fx1(0.50)	600	6
*17	F	35	/	< 0.35	600	6
*18	F	59	/	mx2(1.27); d1(7.52); d2(5.88)	300	6

Note: Food mix FX1; Tree pollen mixed with TX5; Weed pollen mixed with wx7; mixed mold MX2; Egg white f1; Milk F2; wheat f4; Sesame F10; Peanut F13; Soybean F14; crab f23; shrimp f24; Household dust mite d1; dust mite d2; cat dander E1; Dog dander E5; German small sickle i6; Aspergillus fumigatus m3.

Table 2. Comparison of leukocyte count and serum total IgE level during 4 months of omalizumab treatment

	Beginning	Four months	*P*
N	10	10	
Age (Years)	48±15.80		
Total IgE (IU/ml)	437.55±279.35	1071.42±721.28	0.004
Eosinophil %	6.73±5.59	5.55±5.02	0.126
Eosinophil count (× 10^9 cells/L)	0.508±0.53	0.355±0.35	0.064
Basophil %	0.51±0.35	0.50±0.29	0.798
Basophil count (× 10^9 cells/L)	0.04±0.03	0.04±0.03	0.798

levels before omalizumab treatment and after 4 months of treatment, Furthermore, we found that the serum tIgE levels in patients increased from 437.55±279.35 KU/L at baseline to 1071.42±721.28 KU/L after 4 months of treatment (P=0.004) (**Figure 1**).

Trend of serum sIgE in 3 patients

The results in 3 patients with bronchial asthma (Δ marked in **Table 1**) who received omalizumab treatment for more than half a year were further analyzed. The three patients received omalizumab therapy once a month and the serum tIgE was monitored (serum tIgE results in No. 9 patients from 4 to 7 months after the first injection were missing). As shown in **Figure 2**, the serum tIgE in the three patients through the treatment period showed similar trend. The serum tIgE level increased sharply 1 month after first treatment, and then decreased slowly with the extension of treatment times. Even though, the serum tIgE level 8-11 months after the first treatment remained higher than that before treatment.

Changes in the number and ratio of peripheral blood eosinophils and basophils before and after 4 months of omalizumab treatment

An elevated peripheral eosinophil count was shown to be predictive indicator for the severity of asthma [7]. The results showed that there

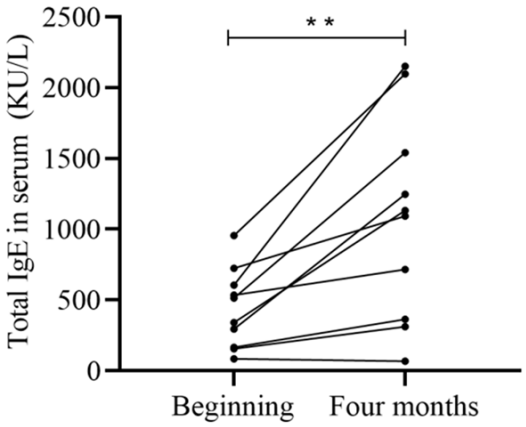

Figure 1. Changes of total IgE level after 4 months of omalizumab treatment.

was a decreasing trend in the proportion and number of peripheral blood eosinophils (5.55± 5.02%, 0.355±0.35 × 10^9 cells/L) after 4 months of omalizumab treatment, compared to that before treatment (6.73±5.59%, 0.508±0.53 × 10^9 cells/L) (see **Table 2**; **Figure 3A** and **3B**). Basophils are effector cells in allergy and also the primary source of IL-4, playing important role in Th2 immune responses [8]. Thus, the number and proportion of basophils were also analyzed. We found that there was no difference in the proportion and number of basophils before treatment (0.51±0.35%, 0.04±0.03 (× 10^9 cells/L)) and 4 months after treatment (0.50±0.29%, 0.04±0.03 (× 10^9 cells/L)) (see **Table 2**; **Figure 3C** and **3D**).

Lung functions before and after omalizumab treatment

Pulmonary ventilation tests are important for diagnosis of asthma with airway obstruction. However, we found that this part of results was incomplete, and only 6 out of 18 patients performed pulmonary function test after omalizumab treatment. In the six patients, the FEV1/FVC ratio increased significantly (P=0.005) after omalizumab treatment (from 65.53± 14.15% to 73.91±13.63%), indicating that the airway obstruction was relieved in omalizumab-treated patients (see **Figure 4**).

Discussion

Asthma is induced by chronic inflammatory disease of the airways, clinically manifested as recurrent wheezing, shortness of breath, with or without symptoms such as chest tightness or cough, accompanied by airway hyperresponsiveness and variable airflow restriction, which can lead to changes in airway structure, i.e., airway remodeling, as the course of the disease prolongs [9]. The mechanism of allergic asthma involves variety of inflammatory cells and mediators, among which IgE is one of the most important molecules. IgE binds to IgE high-affinity receptors on the surface of effector cells (mast cells and basophils), and induces the release of a variety of inflammatory mediators (histamine, tryptase, lipid mediators, cytokines, etc.) by effector cells upon binding with allergens. IgE mediated effector cell activation plays an important role in both immediate and delayed phase of allergic asthma [10]. Omalizumab, a humanized monoclonal antibody against IgE, is the first biologic agent approved for clinical use by the Global Initiative on Asthma (GINA). Omalizumab was reported to reduce allergen-specific Th2 immune response by neutralizing serum free IgE, down regulate surface FcεRI levels of mast cells, basophils, and antigen-presenting cell, and reduce IgE-mediated activation of effector cells (mast cells and basophils) and their release of inflammatory mediators [11, 12]. As early as 2003, omalizumab has been approved by the Food and Drug Administration (FDA) for the treatment of moderate to severe IgE-mediated allergic asthma and chronic spontaneous urticaria (used in the European Union for severe persistent asthma) as an add-on therapy to poorly controlled asthma. And its efficacy and safety have been demonstrated in clinical trials. The drug was approved by the State Food and Drug Administration (CFDA) to be enter China in 2017 and used in clinic since March 2018. The therapeutic efficacy and safety of this drug were the main concern of clinicians, and some related research work was carried out in different regions and hospitals [13, 14].

According to foreign reports, omalizumab showed good efficacy in the treatment of moderate to severe asthma. However, there are also a small number of patients who did not respond well to omalizumab medication (called non-responders), besides the efficacy exist differences among different patients. Since omalizumab is expensive and needs several injections, it may bring a lot of economic burden to asthma patients, especially those with poor

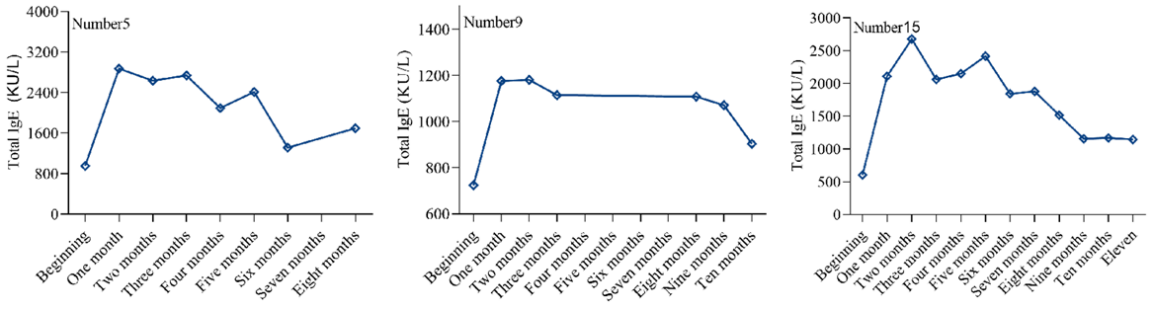

Figure 2. Trend plot of total IgE in serum.

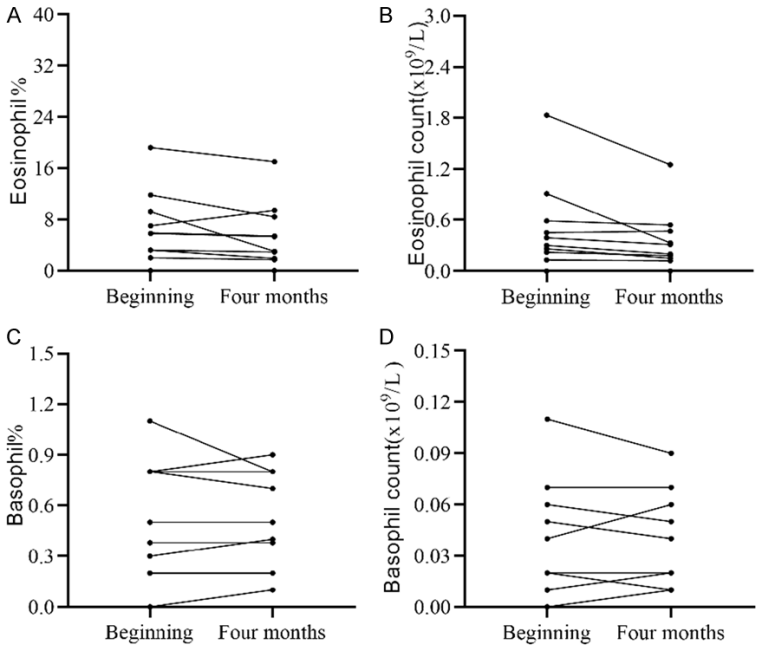

Figure 3. Comparison of the proportion and count of eosinophils and basophils in peripheral Blood of patients before and after 4 months of omalizumab treatment.

efficacy. Thus, to evaluate the effectiveness of omalizumab in the early phase is quite important. However, at present, the clinical efficacy of omalizumab is still based on clinical consultation, which is subjective and sometimes misleading. Thus, objective indicators are in urgent need to evaluate the efficacy of omalizumab.

This study showed that the ratio of moderate to severe asthma patients allergic to dust mite allergy was the highest (55.56%), followed by mixed mold. This is consistent with the results of Huang FL, whose study also showed that more than 50% of asthma patients are allergic to dust mites [15]. However, Liu Hong et al. showed that in bronchial asthma patients the main allergen is dust mites, followed by pollen and then mold, which is slightly inconsistent with the results of this study [16]. We speculated the differences may be induced by age. In this study, the mean age of patients was older, and mold allergy was more common in older patients.

According to the mechanism, omalizumab treatment can reduce the serum free IgE level of patients [17], which should be an important indicator for evaluation omalizumab efficacy. However, the trends of total IgE level after omalizumab treatment is controversial. Ma Wei et al. and Qi Zijiao et al. reported a decrease in serum tIgE level after omalizumab treatment [18]. However, our results showed that serum tIgE levels in most patients after 4 months of treatment were significantly higher than that at the pretreatment baseline (P=0.004), and serum tIgE levels were still higher after more than half a year treatment than baseline. Our results were consistent with the results reported by Haijin Zhao and Shaoxi Cai, which showed that the tIgE of patients responded to omalizumab treatment significantly increased after four weeks of omalizumab treatment, and when the ratio of IgE (at four weeks of treatment)/baseline IgE was greater than 2, the sensitivity of efficacy prediction was as high as 100%, and the specificity was 80% [19]. Elevated serum

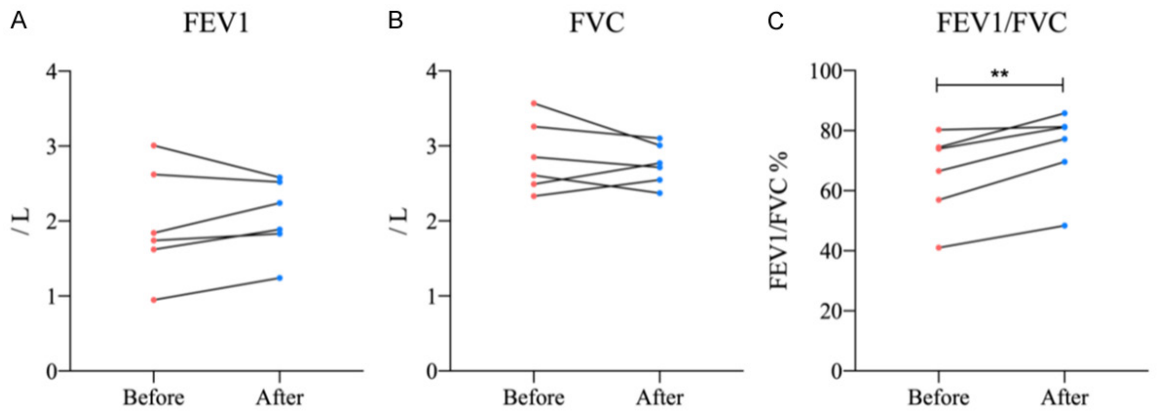

Figure 4. Pulmonary function of patients during 4 months of omalizumab treatment.

IgE following omalizumab therapy may be associated with prolonged half-life of the IgE-omalizumab complex formed [20, 21]. Studies have shown that free IgE has a half-life of 2.4 days, while omalizumab-IgE complex can have a half-life of up to 26 days. Binding of free IgE to omalizumab may result in the deposition of omalizumab and free IgE complexes in blood, and lead to even more than 10 times increase of IgE. In clinical, usually serum tIgE is detected, and it is impossible to distinguish between omalizumab bound and free IgE. According to this, we speculate that the increase in IgE levels at four weeks of treatment further indicate the neutralization of omalizumab to free IgE, and may be an potential indicator for effectiveness evaluation of omalizumab treatment.

Studies have shown that peripheral blood eosinophil levels are associated with clinical symptoms of asthma. In allergic inflammation, eosinophils migrate to the inflammation site, and release intracellular cationic mediators (such as eosinophil cationic protein (ECP), eosinophil peroxidase and major basic protein (MPB)) upon activation. The released mediators can induce epithelial tissue damage and promote airway hyperresponsiveness. The released cytokines such as IL-13 can promotes mucus secretion [7]. Basophils also play an important role in asthma. Studies have shown that basophils are the main source cells of IL-13 and IL-4, which promote the release of CCL11 by endothelial cells and the expression of vascular cell adhesion molecule 1 (VCAM-1). It could promote eosinophil infiltration and the occurrence and development of asthma [22]. Our study showed that there was no significant change in the count and ratio of peripheral blood eosinophil and basophil before and after 4 months omalizumab treatment. The possible reasons may be that: (1) The sample was collected at the stable phase of asthma, when the eosinophil level was at a low level. (2) Omalizumab has no effect on the number of eosinophils or basophils but affects cell function. Poddighe et al. found that omalizumab treatment not only affected the level of FcεRI, a high-affinity receptor for IgE, on the surface of basophils, but also had influence on cell homeostasis, cell responsiveness and cytokine release ability [23]. Caruso C et al. found that the percentage of activated basophils with CD125-expressing were inversely relative to the effectiveness of anti-IL-5/IL-5Rα drugs in patients with eosinophilic asthma [24]. Thus, cell function test may be more important in the evaluation of omalizumab efficacy than cell number.

Pulmonary function test is an important diagnostic and evaluation tool for bronchial asthma [25]. First second forced expiratory volume (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio are the most used parameters to determine the presence or absence of expiratory obstruction. The expected values of FVC and FEV1 ≥ 80% are normal, and the predicted values of FEV1/FVC > 92% are normal. When FEV1/FEV < 70%, it indicates moderate obstructive ventilation changes in the lungs. Our results showed that the FEV1/FVC ratio in asthmatic patients after omalizumab treatment increased (from 65.53% to 73.91%), indicating an improvement in pulmonary ventilation dysfunction. However, many patients did not carry

out regular lung function test, because it is relatively cumbersome for patients making it difficult to be broadly used in clinical.

Since it is a retrospective study, there are a few limitations in this research. First of all, due to the short time for omalizumab to enter China, our hospital started to use the drug since 2020, patients received omalizumab therapy was few. Secondly, as a retrospective study, the clinical data of patients (such as ACT scores, pulmonary function test results and tIgE levels) are incomplete, which makes the data analysis difficult. In another aspect, this reflects the limitations of asthma management system. Some patients do not have realize the importance of optimal asthma control, and treatment is interrupted due to the cost and concerns about adverse effects. In addition, the asthma patients collected are mainly middle-aged and elderly, and adolescents were not rare, which make it impossible to compare the differences at various ages. In our future studies, we will continue to collect patients to expand sample sizes and conduct multicenter studies if necessary. In addition, we will strengthen cooperation with clinician to collect complete data. We hope to explore the trend of cell number, function, and inflammatory mediators after omalizumab treatment to find reliable efficacy evaluation indicators for clinical practice.

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Disclosure of conflict of interest

None.

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