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Original Article

Omalizumab Treatment for Atopic Severe Persistant Asthma: A Single-Center, Long-Term, Real-Life Experience with 38 Patients

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Abstract

OBJECTIVES: Omalizumab is a monoclonal antibody that is used as add-on therapy for treating moderate-to-severe persistant atopic asthma in patients with persistant symptoms and frequent exacerbations, despite step 4 treatment according to GINA guidelines. Real-life studies on omalizumab treatment are limited in Turkey. Thus, the present study aims to assess the clinical efficacy and treatment outcomes of omalizumab in patients with atopic severe persistant asthma.

MATERIALS AND METHODS: Patients with atopic severe persistant asthma who were treated with omalizumab between 2009 and 2017 were retrospectively evaluated. Baseline and last results of the following variables were compared: symptom scores (GINA categorical), controller medications, blood eosinophil counts, forced expiratory volume in 1 second (FEV_1) values, and the number of exacerbations that were treated with systemic corticosteroids for at least 3 days within the last 1 year. The effect of coexisting aspirin-exacerbated respiratory disease (AERD) on these parameters was also analyzed. Step-down of other asthma medications was attempted in patients with symptom control and in those without an exacerbation history within the last 6 months.

RESULTS: Thirty-eight patients (mean age, 50 years; females, 30) were included in this study, of whom four showed AERD. After treating with a mean time of 30±22.1 (min: 6, max: 92) months, 26 (68%) patients showed complete controlled disease and 12 (32%) showed partly controlled disease, of whom all had uncontrolled disease before. Mean exacerbation rates within the last 1 year decreased by approximately 76% (9.4±8.4 vs. 1.8±1.5; p<0.001) and FEV_1 values increased by approximately 14% (2075±729 vs. 2321±800 cc; p=0.001) compared with baseline levels. Although the reduction in eosinophil count was not significant in all patients (503.8±524.8 vs. 370.8±314.5; p=0.134), repeated measures analysis of variance revealed a more prominent reduction in eosinophil count in the AERD group than in the non-AERD group, independent from the treatment period (F: 4.23, p=0.049). The mean inhaled corticosteroid dose (budesonide eq., 1063±397 vs. 958±439 mcg; p=0.084), the number of other controller medications, and the number of patients with long-term systemic steroid use decreased after omalizumab treatment. No serious adverse events were recorded during the follow-up period.

CONCLUSION: Our results confirm that omalizumab significantly improves disease control and is a safe add-on therapy. In addition, in suitable patients with controlled disease over time, the step-down of other asthma medications will be appropriate.

KEYWORDS: Severe asthma, allergic asthma, therapy management, anti-IgE, omalizumab

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INTRODUCTION

Asthma is a chronic respiratory disease characterized by variable symptoms and airflow limitation; it is usually associated with chronic airway inflammation and hyperresponsiveness [1]. A subgroup within the asthmatic population is at a high risk for complications, uncontrolled disease, and exacerbations. The patients in this subgroup are classified as having severe asthma, and it is estimated that severe asthma accounts for approximately 3.6% of individuals with asthma [2].

Severe asthma is defined as a disease that remains uncontrolled despite high-dose (>800 mcg budesonide) inhaled corticosteroids (ICS) and long-acting β2-agonist (LABA) or leukotriene modifier/theophylline treatments in the previous year or systemic corticosteroid treatment for at least half of the past year, or asthma that can only be controlled with these treatments [3]. Some phenotype-based add-on treatments are available for treating severe asthma. Omalizumab (Xolair; Novartis, Switzerland) is a humanized anti-IgE monoclonal antibody (mAb) approved as an add-on treatment to ICS/LABA for patients with atopic moderate or severe asthma that is uncontrolled with step 4 treatment [1]. The efficacy of omalizumab in patients with atopic severe persistant asthma has been shown in many randomized clinical trials and real-life data stud-

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ies [4-6]. Previous studies have reported a positive effect of omalizumab on symptom control, lung function, and quality of life, and omalizumab has been found to reduce ICS use, systemic corticosteroid (SCS) use, and the number of severe exacerbations. It has been shown that patients with a positive therapeutic effect are likely to exhibit a sustained response that may extend up to 2-4 years after discontinuation [5].

Although omalizumab is approved in our country since 2008, studies on treatment outcomes in the Turkish patient population are limited [7-10]. Hence, the present study aims to evaluate the clinical efficacy of omalizumab in a real-life setting. In addition, the reduction or withdrawal of ICS and/or other asthma medications during omalizumab therapy, was also investigated.

MATERIALS AND METHODS

The records of adult (>18 years) patients with atopic severe persistant asthma who were treated with omalizumab for >6 months in 2009-2017 at a referral university hospital were retrospectively analyzed. Adherence, inhaler technique, and coexisting conditions that may intervene with disease control were investigated in all the patients. All the patients showed serum IgE levels within the recommended range for omalizumab treatment and positive test results demonstrating at least one perennial allergen sensitization.

Data on demographics, baseline serum total IgE levels, and allergen sensitization status of the patients were collected from the charts. In addition, for each patient, we noted baseline and last results for the following variables: all asthma medications, symptom control measures, blood eosinophil counts, forced expiratory volume in 1 second (FEV_1) values, and the number of exacerbations that required SCS for at least 3 days (either ER admission, outpatient clinic visit, or hospitalization) within the last 1 year (only for the patients who were treated for more than 1 year with omalizumab). ICS and SCS were presented as their budesonide and methyl-prednisolone equivalents, respectively. Symptom control was assessed by the GINA symptom control tool wherein the frequency of daytime symptoms, night waking, reliever treatment use, and activity limitation in the past 4 weeks was questioned at each follow-up [1]. For these four questions, three or four positive answers was accepted as uncontrolled, one or two positive answers as partially controlled, and all negative as well controlled. To establish the effect of omalizumab on disease prognosis more efficiently, basal and last measures of symptom scores, laboratory and FEV_1 parameters were obtained from the patients' exacerbation-free periods. An exacerbation was defined as the acute worsening of symptoms and lung functions from the usual status of the patient that requires unscheduled medical care and increase in daily medications [1].

Patients received appropriate dosage and intervals based on an omalizumab dosing chart that used the serum total IgE levels and body weight. All injections were performed by nurses with experience in the allergy clinic. Omalizumab was continued in patients who were considered to benefit from the treatment at the end of 16 weeks. Omalizumab was discontinued at the end of 5 years and reinitiated if the patient was still symptomatic despite other therapies on their follow-up. While calculating the total treatment period, these omalizumab-free periods were subtracted. Reactions that may have been associated with the drug were recorded.

In well-controlled and exacerbation-free patients over 3-6 months, first, SCS withdrawal was attempted, which was followed by long-acting muscarinic antagonist, montelukast, and theophylline according to the GINA counter-stepwise approach. Further, stepping down to the lowest ICS/LABA dose was attempted if the patient was still well controlled for every 3-6 months. LABA discontinuation was attempted only if the patient was constantly well controlled and exacerbation-free for at least 6 months. The last stabilizing treatment dose was re-established when patients became symptomatic. Complete ICS withdrawal was not attempted in any patient. Patients whose inhaler steroid dose could (ICS dose could be permanently reduced from baseline for at least 6 months) and could not be reduced permanently were also compared. Due to the retrospective design of this study, written informed consent was not obtained. This retrospective study fully conformed to the principles of the Declaration of Helsinki and does not require ethics approval [11].

Statistical Analysis

Data recording and statistical analyses were performed using SPSS (Statistical Package for Social Sciences) version 17.0 (SPSS Inc.; Chicago, IL, USA). Distribution of the data was established using the Kolmogorov-Smirnov test. Numerical data were expressed as mean±standard deviation (SD) or median (25^{th}-75^{th} percentile) according to the distribution of the variable. Paired sample t-test was performed to test the differences between pre- and post-treatment. Between-group comparisons were performed using independent sample t-test, Mann-Whitney U-test, or chi-square test, as appropriate. Repeated measures analysis of variance was used to demonstrate the effect of aspirin-exacerbated respiratory disease (AERD) on the change in peripheral eosinophilia. A $p<0.05$ was considered significant.

RESULTS

Of the 38 patients included in the present study, 30 were female. Mean age was 50±10.8 years. All the patients had at least one perennial allergen sensitization. Median basal serum IgE level was 173 IU/mL (101.8-410), and mean blood eosinophil count was 503.8±524.8 cells/mL (Table 1). Four patients showed AERD.

The baseline mean inhaler steroid dose was 1063±397 mcg. Patients' treatments are summarized in Table 2. The patients who had uncontrolled asthma (mean categorical scores, 3.6±0.5) despite these therapies were administered omalizumab for a mean of 30±22.1 months (min: 6, max: 92; <1 year=6 patients, 1-3 years=20 patients, and 3-5 years=12 patients). The last symptom scores decreased by 87% (Table 3). In total, 68% of patients who had uncontrolled disease prior to omalizumab treatment had well-controlled disease in their last visit. The mean number of systemic steroid-requiring exacerbations per year decreased from 9.4±8.4 to 1.8±1.5, and FEV_1 values increased from 2075±729 to 2321±800 cc ($p<0.001$ and $p=0.001$, respectively). Blood eosinophil count decreased by 13%, but the difference was not significant. Repeated measures analysis of variance showed a more prominent reduction in eosinophil count in the AERD group than in the non-AERD group, independent from the treatment duration (F: 4.23, $p=0.049$) (Figure 1).

Table 1. Patient characteristics and clinical findings at baseline

	N=38
Age, years±SD	50±10.8
Female gender, n (%)	30 (79)
Median serum total IgE, IU/mL±SD	173 (101.8 - 410)
Serum eosinophil count, cells/mL±SD	503.8±524.8
Upper respiratory tract involvement, n (%)	
None	5 (13)
Chronic rhinitis	29 (76)
AERD	4 (11)
Treatment duration, months±SD	30±22.1
Allergen sensitization status, n (%)	
Mite	31 (82)
Pollen	11 (29)
Dander	2 (5)
Mold	15 (40)
Single allergen sensitization	17 (45)

SD: standard deviation; AERD: aspirin-exacerbated respiratory disease

While seven patients were receiving long-term systemic steroid treatment before omalizumab (sum of daily SCS need for seven patients was 57 mg; mean, 8.1 mg per patient), the number decreased to two at the last visit (sum of daily SCS need for two patients was 8 mg; mean, 4 mg per patient). Budenoside-equivalent inhaler steroid doses also decreased

Table 2. All baseline and last controller medications

	Baseline	Last	p
ICS dose*, mcg±SD	1063±397	958±439	0.084
Other controller medications, n (%)			
LABA	38 (100)	37 (97)	>0.05
Montelukast	34 (90)	30 (79)	
Theophylline	8 (21)	3 (8)	
LAMA	9 (24)	7 (18)	
Total dose of long-term SCSs, mg/day**	57 (n=7)	8 (n=2)	-

ICS: inhaled corticosteroid; SD: standard deviation; LABA: long-acting β2-agonist; LAMA: long-acting muscarinic antagonist; SCS: systemic corticosteroid

*: Budesonide equivalent; **: Represented as the sum of all the patients' daily SCS dosage as methyl-prednisolone equivalent

Table 3. Comparison of the baseline and last symptom scores, exacerbation rates, FEV_1 values, and eosinophil counts

	Baseline	Last	Mean change from baseline	p
Symptom scores (GINA)	3.6±0.5	0.5±0.7	-87%	<0.001
Complete control, n (%)	0	26 (68)		
Partial control, n (%)	0	12 (32)		
Uncontrolled, n (%)	38 (100)	0		
The number of exacerbations that required SCS for at least 3 days within the last 1 year±SD (n=32)	9.4±8.4	1.8±1.5	-76 %	<0.001
FEV_1, % predicted±SD	77±18.9	86.9±21.2	15%	0.001
FEV_1, cc±SD	2075±729	2321±800	14%	0.001
Serum eosinophil count, cells/mL±SD	503.8±524.8	370.8±314.5	-13%	0.134

SCS: systemic corticosteroid; FEV_1: forced expiratory volume in 1 second; SD: standard deviation

Table 4. Comparison of patients that inhaled corticosteroids could and couldn't be reduced permanently

	ICS dose permanently reduced (n=10)	No reduction in ICS dose (n=28)	p
Female gender, n (%)	7 (70)	23 (82)	0.4
Age, years±SD	54±9.8	48.6±11	0.2
Treatment duration, months±SD	28±21.7	31.9±25.6	0.67
Baseline median serum total IgE, IU/mL±SD	163 (102-230)	173 (95-467)	0.42
Baseline FEV_1 values, cc±SD	1997±733	2104±740	0.7
Change in FEV_1, cc±SD	301±234.7	212.6±470	0.57
Baseline serum eosinophil count, cells/mL±SD	525±340	497.3±575.3	0.9
Change in serum eosinophil count, cells/mL±SD	-71.3±398	-229.2±534	0.45
Last ICS dose, mcg±SD	600 (350-800)	800 (800-1600)	0.002
The number of exacerbations that required SCS for at least 3 days within the last 1 year±SD	0.78±1.1	1.93±1.5	0.04

ICS: inhaled corticosteroid; SD: standard deviation; FEV_1: forced expiratory volume in 1 second; SCS: systemic corticosteroid

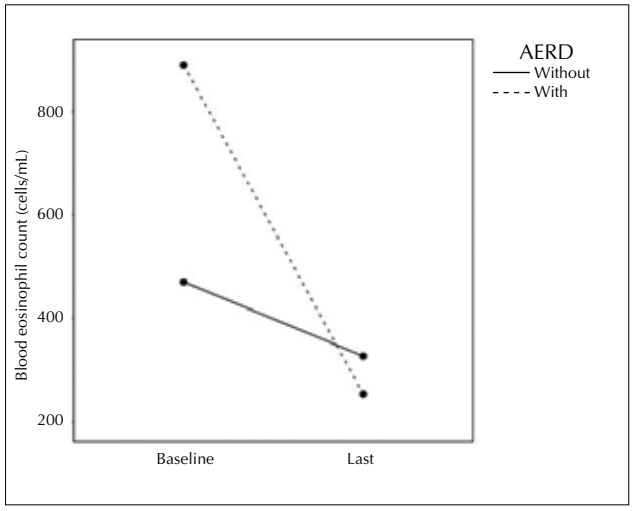

Figure 1. The aspirin-exacerbated respiratory disease (AERD) group showed a more prominent reduction in the eosinophil count [median, -600 (-850-460) vs. -10 (-240-130)]. This reduction was independent of the duration of treatment (F: 4.23, p=0.049). However, symptom scores, exacerbation rates, and the number of ICS-reduced patients were not different between the AERD and non-AERD groups

compared with baseline (1063±397 vs. 958±439 mcg, respectively; p=0.084). In 10 patients, besides other controller medications, inhaler steroid doses could be reduced permanently. The number of systemic steroid-requiring exacerbations in the last year was significantly lower in these patients (0.8±1.1 vs. 1.9±1.5; p=0.04) (Table 4). However, there was no significant difference between these groups in terms of demographic, clinical, physiological, or laboratory parameters. All other controller medications, except inhaler steroids, could be discontinued in only one patient who was well controlled and exacerbation-free for 1 year. ICS doses could not be reduced in any patient with AERD.

Omalizumab treatment was terminated at the fifth year in three patients. Because they were again symptomatic after 12 and 18 months, omalizumab was reinitiated in two of these patients. Omalizumab was well tolerated in all patients throughout the therapy, and no systemic reactions or serious adverse events were recorded during the follow-up period.

DISCUSSION

Our results show that omalizumab add-on therapy for 30 months is an efficient therapy in patients with atopic severe persistant asthma in real-life settings. With omalizumab, the systemic corticosteroid-requiring exacerbation rate decreased by 76%, and basal FEV_1 values increased by 14%. Of all the patients who had uncontrolled disease prior to omalizumab treatment, 68% and 32% showed well controlled and partly controlled disease, respectively, after the treatment. In addition, step-down therapy from ICS and other controller medications was managed in some patients.

The effect of omalizumab in patients with severe persistant allergic asthma has been shown in many randomized clinical trials and real-life data studies [4-6]. Similar to our study, these studies also reported symptom control, improved lung function, and improved quality of life, as well as reduced ICS and SCS use and the number of severe exacerbations. In a study by Alfarroba et al. [12], which also used GINA categorical symptom control classification, 54% of all patients with uncontrolled disease improved to well-controlled disease at the end of a 24 month-therapy. In their cross-sectional, national observational study on patients receiving omalizumab therapy in Italy, Novelli et al. [13] evaluated the level of control according to the GINA classification and reported 25.2% of patients with well-controlled disease and 47.1% of patients with partially controlled disease at the end of a 32 month-therapy (median). Similar to GINA scores, 66% of patients had asthma control test (ACT) scores ≥20. Another study that used ACT scores for evaluation demonstrated a 65% improvement with omalizumab therapy at the end of 3 years [14]. A real-life observational study also reported an increase in ACT scores from 10.4 to 20.4 with omalizumab treatment in Turkey [7].

Besides symptom control, omalizumab also has an effect on exacerbation and hospital admission rates and improves the quality of life. Our study showed a 76% decrease in mean steroid-requiring exacerbation per year from 9.4±8.4 to 1.8±1.5. Our baseline mean exacerbation rates were higher than those reported in the literature; this is because our values included all exacerbations-hospitalization, ER admission, or outpatient clinic visit-that require at least 3 days of SCS treatment. In a meta-analysis of real-life studies, a decrease in exacerbation rates after 1 year of treatment with omalizumab was reported, which was 46%-80% [5]. López-Tiro et al. [14] reported a 95% decrease in hospitalization and an 80% decrease in ER admissions after 1 year of treatment as well. Another important result of our study is the 14% (approximately 250 cc) increase in FEV_1 values with the treatment. FEV_1 increase was not correlated with the duration of treatment (min: 6, max: 92 months). Previous real-life data studies have also shown an 8%-33% increase in FEV_1 values after 1 year of omalizumab treatment [5]. More importantly, Özgür et al. [10] noted a 24.5% increase in FEV_1 values at the first year, which persisted beyond 3 years (20.4% at the last visit beyond 36 months).

Previous studies have shown that peripheral blood eosinophilia may be an important marker for the clinical response to omalizumab [15]. In their placebo-controlled study, Hanania et al. [16] reported that following omalizumab treatment, the mean reduction in the exacerbation rate was only higher in patients with a higher baseline peripheral eosinophil count (>260/μl). Another study showed that a peripheral eosinophil count of >300/μL can predict a better treatment response [17]. Apart from this relationship between baseline eosinophil count and treatment response, decreased peripheral eosinophil count was also noted with omalizumab treatment. In a pooled analysis of data from five randomized controlled trials, Massanari et al. [18] found that post-treatment eosinophil counts were significantly reduced in the treatment group. They also found similar results in patients with pre-treatment SCS use. Although the eosinophil count dropped with omalizumab treatment in our study, the difference was not statistically significant. This could be due to our small sample size and the higher baseline eosinophil levels of our patients compared with previous studies. Interestingly, despite our small

sample size, the eosinophil count drop was significantly higher in patients in the AERD group than in those in the non-AERD group. However, the ICS dose was not reduced in any of these patients; symptomatic scores and decrease in the exacerbation rates were also similar to the other patients. Although omalizumab markedly decreased the eosinophil counts in these patients, these findings suggest that clinical effects occur via mechanisms other than eosinophil count decrease. In addition, even though the blood eosinophil count decreases, it is still unclear how it affects tissue eosinophilia; therefore, it would be speculative to comment on the clinical effects of this decrease.

First-line controller therapy involves ICS, and up-dosing is recommended, up to long-term systemic steroids, if the disease cannot be controlled otherwise. The primary advantage of mAbs, which act through the Th-2 pathway, is their steroid-sparing effects, and the disease can be controlled without any possible steroid-related side effects [19]. It has been proposed that long-term omalizumab treatment has disease-modifying effects, but this is still arguable [20, 21]. Therefore, despite several previous studies, we do not completely discontinue ICS in any patient with atopic severe persistant asthma who receives omalizumab therapy. However, we try to use the controller medications in the lowest dose possible as long as the patient is under control with omalizumab. As expected, patients whose ICS dose could be reduced also had lower exacerbation rates at the last year, but no other difference was found between the patients whose ICS dose could be and could not be reduced. There are controversial data on ICS and SCS dose reduction/withdrawal in the literature. A Cochrane meta-analysis reported no significant difference between omalizumab and placebo groups in terms of the median reduction of daily SCS and also the number of participants that were able to withdraw SCS. Interestingly, ICS reduction or withdrawal was significantly more likely in patients who received omalizumab treatment [4]. In another meta-analysis based on real-life data, ICS reduction rates in 1 year were 10%-28% [5]. Bavbek et al. [7] also reported a significant decrease in SCS and other asthma drug dosages but no difference in ICS doses at the end of 15 months (median). It should be noted that a marked heterogeneity exists in both patient characteristics and methodology in these studies. However, based on our findings, we suggest that for patients who are asymptomatic and exacerbation-free under omalizumab treatment, asthma medications other than ICS should be decreased and withdrawn, if possible, starting with SCS, as a counter-stepwise approach. If the patient is still stable, the ICS dose should also be reduced.

In conclusion, this study presents our 8-year experience of omalizumab treatment in patients with atopic severe asthma. Our results show a significant decrease in symptom scores, the number of exacerbations that required SCS for at least 3 days, and systemic steroid requirement, as well as improved FEV_1 values, after omalizumab treatment. In addition, step-down was possible in a quarter of the patients, and ICS could be permanently reduced under omalizumab treatment. Our study may also contribute to the method of step-down of asthma treatments in patients under omalizumab treatment.

Ethics Committee Approval: This retrospective study fully conformed to the principles of the Declaration of Helsinki and does not require ethics approval.

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

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REFERENCES

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2017. Available from: www.ginasthma.org. Accessed November 25, 2017.
2. Hekking PP, Wener RR, Amelink M, et al. The prevalence of severe refractory asthma. J Allergy Clin Immunol 2015;135:896-902. [CrossRef]
3. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-73. [CrossRef]
4. Normansell R, Walker S, Milan SJ, et al. Omalizumab for asthma in adults and children. Cochrane Database Syst Rev 2014;1:CD003559.
5. Abraham I, Alhossan A, Lee CS, et al. 'Real-life' effectiveness studies of omalizumab in adult patients with severe allergic asthma: systematic review. Allergy 2016;71:593-610. [CrossRef]
6. Alhossan A, Lee CS, MacDonald K, Abraham I. "Real-life" Effectiveness Studies of Omalizumab in Adult Patients with Severe Allergic Asthma: Meta-analysis. J Allergy Clin Immunol Pract 2017;5:1362-70. [CrossRef]
7. Bavbek S, Aydın Ö, Kepil Özdemir S, et al. Therapy with omalizumab in patients with severe persistant allergic asthma: a real life data in Turkey. Tuberk Toraks 2010;58:425-34.
8. Tat TS, Çilli A. Omalizumab treatment in patients with severe allergic asthma. İstanbul Med J 2017;18:135-8. [CrossRef]
9. Bilgir F, Özdemir B, Değirmenci P, et al. Our anti-IgE (omalizumab) experience in severe allergic asthma: 1st year experience. İzmir Göğüs Hastanesi Dergisi 2017; 3: 165-71.
10. Özgür ES, Özge C, İlvan A, et al. Assessment of long-term omalizumab treatment in patients with severe allergic asthma long-term omalizumab treatment in severe asthma. J Asthma 2013; 50: 687-94. [CrossRef]
11. National Code on Clinical Researches published in Official Gazette numbered with 28617 at Apr 13, 2013. Available at: http://www.resmigazete.gov.tr/main.aspx?home=http://www.resmigazete.gov.tr/eskiler/2013/04/20130413.htm&main=http://www.resmigazete.gov.tr/eskiler/2013/04/20130413.htm. Accessed Feb 13, 2018.
12. Alfarroba S, Videira W, Galvão-Lucas C, et al. Clinical experience with omalizumab in a Portuguese severe asthma unit. Rev Port Pneumol 2014; 20: 78-83. [CrossRef]

13. Novelli F, Latorre M, Vergura L, et al. Asthma control in severe asthmatics under treatment with omalizumab: a cross-sectional observational study in Italy. Pulm Pharmacol Ther 2015; 31: 123-9. [CrossRef]
14. López Tiro JJ, Contreras EA, del Pozo ME, et al. Real life study of three years omalizumab in patients with difficult-to-control asthma. Allergol Immunopathol (Madr) 2015; 43: 120-6. [CrossRef]
15. Kupryś-Lipińska I, Molińska K, Kuna P. The effect of omalizumab on eosinophilic inflammation of the respiratory tract in patients with allergic asthma. Pneumonol Alergol Pol 2016; 84: 232-43. [CrossRef]
16. Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy. Ann Intern Med 2011; 154: 573-82. [CrossRef]
17. Zierau L, Walsted ES, Thomsen SF, et al. Response to omalizumab in patients with severe allergic asthma: A real-life study. Respir Med 2017; 131: 109-13. [CrossRef]
18. Massanari M, Holgate ST, Busse WW, et al. Effect of omalizumab on peripheral blood eosinophilia in allergic asthma. Respir Med 2010; 104: 188-96. [CrossRef]
19. Domingo C, Moreno A, Mirapeix R. Rationale for the use of immunomodulatory therapies in the Global Initiative for Asthma (GINA) step V asthma other than oral glucocorticosteroids. Intern Med J 2011; 41: 525-36. [CrossRef]
20. Nopp A, Johansson SG, Ankerst J, et al. CD-sens and clinical changes during withdrawal of Xolair after 6 years of treatment. Allergy 2007; 62: 1175-81. [CrossRef]
21. Lowe PJ, Renard D. Omalizumab decreases IgE production in patients with allergic (IgE-mediated) asthma; PKPD analysis of a biomarker, total IgE. Br J Clin Pharmacol 2011; 72: 306-20. [CrossRef]