

Real-world data evaluation of total IgE, specific IgE and omalizumab therapy in a cohort of allergic asthma patients treated in a community-based practice

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Abstract

Objective

In this study, we: (1) evaluated the correlation between total IgE and the presence of specific IgE; (2) compared the characteristics of patients with positive specific IgE to those with negative specific IgE; and, (3) analyzed the allergic testing results of patients on omalizumab and reported the effect of omalizumab on forced expiratory volume (FEV₁) and asthma control test (ACT) results.

Methods

Data from patients diagnosed with allergic asthma and seen at Florida Lung, Asthma & Sleep Specialists (FLASS) between January 2016 and June 2019 were analyzed. Parameters evaluated were total IgE, and levels of specific IgE to antigens in the ImmunoCAP test and skin prick test (SPT). Additional parameters for patients on omalizumab therapy for at least 6 months were FEV₁, % predicted FEV₁ and ACT results.

Results

A total of 475 patients (114 males, 361 females) met the inclusion criteria. The mean age was 53 years (range: 17 to 89 years). Of these, 36 patients were not included in the analysis due to incomplete data.

- Mean total IgE was higher in patients with positive ImmunoCAP results compared to those with negative results (396 KU/L vs. 81.3 KU/L).
- There was a significant positive correlation between total IgE and levels of positive specific IgE in the ImmunoCAP test ($p < 0.0001$, $r = 0.36$, $n = 213$ patients).
- The correlation between total IgE and levels of positive allergens in SPT was not significant ($p = 0.15$, $n = 44$ patients)

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- Two positive reactions to allergens were seen in 22% of ImmunoCAP tests and 13% of SPT tests.
- There was no statistically significant improvement in FEV₁ (p=0.097, CI -0.17 to 0.02) and % predicted FEV₁ (p=0.109, CI -6.63 to 0.70) in patients who used omalizumab for at least 6 months.
- There was a statistically significant improvement in ACT scores (p=0.031, CI -4.21 to -0.21) in patients who used omalizumab for at least 6 months.

Conclusion

Allergic asthma could be seen in patients who had an absence of specific IgE in ImmunoCAP and a negative reaction to SPT. The benefit of omalizumab therapy is not limited to allergic asthma patients with positive specific IgE.

Keywords: Allergic asthma; Total IgE; Specific IgE; ImmunoCap; Skin prick test; Omalizumab.

Introduction

Asthma is a common condition characterized by airway inflammation and bronchial hyperresponsiveness, which affects about 25 million people in the USA [1]. Allergic asthma, the most common phenotype, accounts for approximately 60% of asthma cases in adults [2,3]. Although the eosinophilic phenotype is more common among the severe cases of asthma [4], there is considerable overlap between atopic asthma and eosinophilic asthma [5]. Atopic asthma is characterized by the presence of IgE antibodies against common allergens. When these allergens cross-link specific IgE bound to high-affinity IgE receptors on the surface of basophils and mast cells, pro-inflammatory mediators have released that trigger and perpetuate airway symptomatology. The diagnosis of allergic asthma is made by the presence of serum specific IgE levels (ImmunoCap) or a positive skin prick test (SPT) and elevated total IgE levels. There is a strong correlation between elevated total IgE levels and allergic asthma [6]; this correlation is still present in those with negative specific IgE levels [7].

Furthermore, a low level of total IgE does not exclude the presence of specific IgE [8].

There has been a significant change in the management of severe asthma with the advent of biologics that target different biomarkers involved in asthma pathogenesis. Omalizumab is a humanized monoclonal antibody (IgG1k) that binds specifically to human IgE [9]. It was the first biologic approved for the management of allergic asthma that is not controlled with inhaled corticosteroids. Omalizumab inhibits the binding of IgE to high-affinity IgE receptors (FcεRI) on the surface of mast cells and basophils. Treatment with omalizumab also reduces the number of high-affinity IgE receptors on basophils [10]. Omalizumab is indicated for adults or adolescents (12 years of age and above) with moderate-to-severe persistent asthma who have a positive skin test or in-vitro reactivity to a perennial aeroallergen.

The dosing of omalizumab is based on body weight and baseline serum total IgE concentration. In the preapproval phase 3 trials, subjects are required to have a baseline IgE of between 30-700 IU/mL and a bodyweight of not more than 150 kg. The

full prescribing information did not specify the class level of skin reactivity that is considered positive nor the level of specific IgE considered to be clinically significant. Specific IgE levels higher than 0.35 KU/L suggest sensitization but is not synonymous with the clinical disease [11]. The interpretation of skin-prick testing varies among allergists who, ideally through training, are supposed to be better at performing and interpreting allergic skin tests [12]. The way pulmonologists interpret allergy skin tests and ImmunoCap testing and how the results are being used to determine who is a candidate for omalizumab therapy is unknown.

In this retrospective study, performed in a single, specialized community-based practice, we sought to investigate the following areas: (1) Evaluate the correlation between total IgE and specific IgE level; (2) Compared the characteristics of patients with positive specific IgE from those with negative specific IgE; (3) Analyze the allergic testing results of patients on omalizumab and report the effect of omalizumab on the asthma control test (ACT).

Method

All patients with a diagnosis of allergic asthma seen at Florida Lung, Asthma & Sleep Specialists (FLASS) between January 2016 and June 2019 were evaluated to be included in the analysis. A minimum of six months of follow-up was required to be included in the study, so patients seen after December 2018 were excluded from the analysis. To be included in the study, the patients must have had elevated IgE level $\geq$ 100 KU/L or at least one positive specific IgE on ImmunoCap or SPT. Asthma patients on omalizumab were

automatically included in the dataset if they had been undergoing therapy for at least six months.

Demographic variables captured for analysis included age, sex, and race. In addition, clinical data collected included total IgE, a number of positive specific IgE to allergens on ImmunoCap and SPT. ImmunoCap is a blood antibody test that measures the concentration of specific IgE to allergens which is a test for sensitization to hundreds of allergens. ImmunoCap positivity is based on a value of 0.35 KU/L or greater and, likewise, SPT is considered positive if the wheal is greater than 3mm above the negative control.

We also recorded the FEV₁ and ACT score of patients on omalizumab therapy before they began treatment and then after at least 6 months of therapy. The ACT is a validated, five-item, patient-completed measure of asthma control with a recall period of four weeks. The ACT is a reliable, valid, and responsive questionnaire for assessing asthma control. A cut-off score of 19 or greater identifies patients with adequately controlled asthma.

The statistical analysis of results was performed using a statistical package for the social sciences (SPSS) version 26 and formulated into figures and tables. The ACT and FEV₁ values pre- and post-omalizumab therapy were compared utilizing the paired T-test for statistical significance (a p-value less than or equal to 0.05 was considered statistically significant). The Pearson correlation coefficient is used to calculate the association between total IgE and specific IgE levels.

Results

A total of 475 patients seen at FLASS between 2016 and 2019 met the criteria for evaluation. The mean age at the time of the study was 53 years (range: 17-89 years) Table 1 describes the age, self-declared

race, and a breakdown of the patients based on ImmunoCap or allergy skin test results. Of these, 431 (90%) of the patients had ImmunoCap results and 36 patients were excluded due to incomplete data. Of note, 75% of the cohorts were female.

Table 1: Summary of the demographic data of the 475 allergic asthma patients studied.

Tests undergone	ImmunoCap test	Skin prick test (SPT)	Total
Description			
Males (n)	104	10	114
Females (n)	327	34	361
Total number of patients	431	44	475
Mean Age	53years (Range: 17 to 89 years)	51years (Range: 19 to 79)	52.8years (Range: 17 to 89 years)
Race			
African American	27	1	28
Caucasian	334	34	368
Others	70	9	79
Unanalyzed Patients (incomplete data)	36	0	36
Patients analyzed			
Males (n)	96	10	106
Females (n)	299	34	333
Total	395	44	439

Table 2 shows the characteristics of the patients with an elevated IgE level who underwent ImmunoCap. 54% had positive

ImmunoCap with a mean total IgE level of 395.7 KU/L compared to 81.3 KU/L in those patients with negative Immunocap.

Table 2: Summary of ImmunoCap test results for the 395 allergic asthma patients analyzed.

Description	Results
Positive ImmunoCap Tests	N=213
Negative ImmunoCap Tests	n=182
Highest frequency number of positive antibodies on ImmunoCap	2 (Seen in 22% of 213 positive patients)
Mean Total IgE of all 395 analyzed patients	250.8 KU/L
Mean Total IgE of ImmunoCap-positive patients (213)	395.7 KU/L
Mean Total IgE of ImmunoCap-negative patients (182)	81.3 KU/L
Pearson correlation between total IgE and number of positive antibodies on ImmunoCap test	p<0.0001 (significant correlation) r=0.36 (positive moderate strength)

Figure 1: Bar chart showing the frequency of positive ImmunoCap test results.

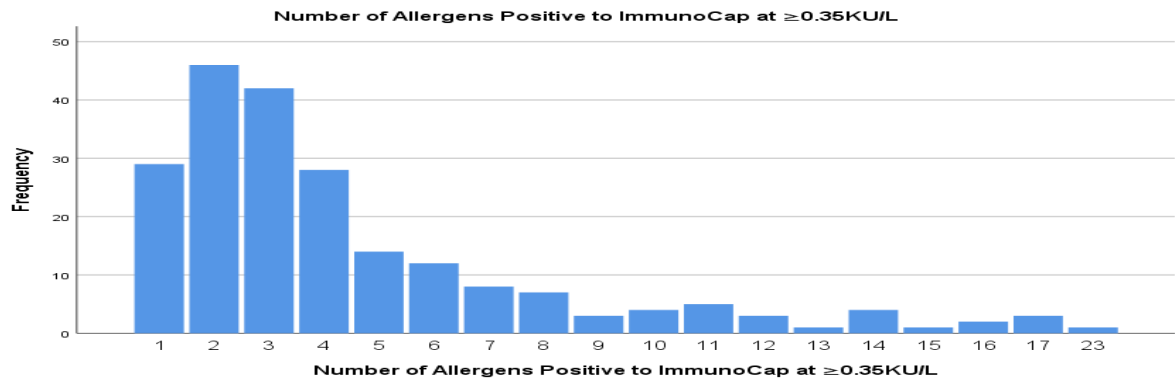


Figure 1 displays the frequency of the number of allergens positive on ImmunoCap per patient. The most frequent is two, seen in 22% of the patients with positive ImmunoCap.

Figure 2: Scatter plot graph of positive ImmunoCap against total IgE

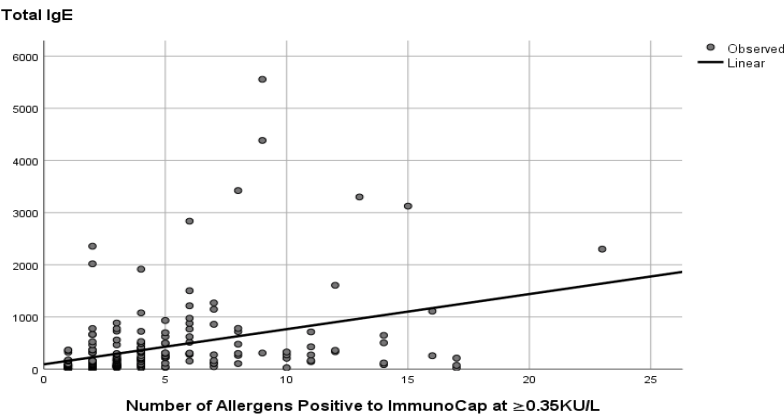


Figure 2 reveals the straight-line slope estimate between the total IgE and specific IgE of the patients. 13% of the variation in specific IgE can be explained by the total IgE level. (since $R^2=0.13$)

Table 3: Summary of skin prick test (SPT) results in 44 allergic asthma patients.

Description	Results
Positive skin prick Test	N=38
Negative ImmunoCap Test	n=6
Highest frequency number of positive SPT results	2 (Seen in 13% of 38 SPT positive patients)
Mean Total IgE of all 44 patients	160.4KU/L
Mean Total IgE of SPT-positive patients (38)	147.5KU/L
Mean Total IgE of SPT-negative patients (6)	241.5KU/L
Pearson correlation between total IgE and number of Positive SPT	p=0.15 (not significant)

Table 3 shows the characteristics of the patients who underwent SPT. 86% tested positive, with females being predominant as in ImmunoCap testing. The mean IgE was lower amongst those testing positive for SPT in comparison to those testing

negative. No significant correlation was noted between SPT and total IgE levels.

Figure 3 displays that in patients testing positive for SPT, two positive allergens occurred most frequently, in 13% of the SPT-positive cohort.

Figure 3: Bar chart showing frequency of positive allergens on skin prick test.

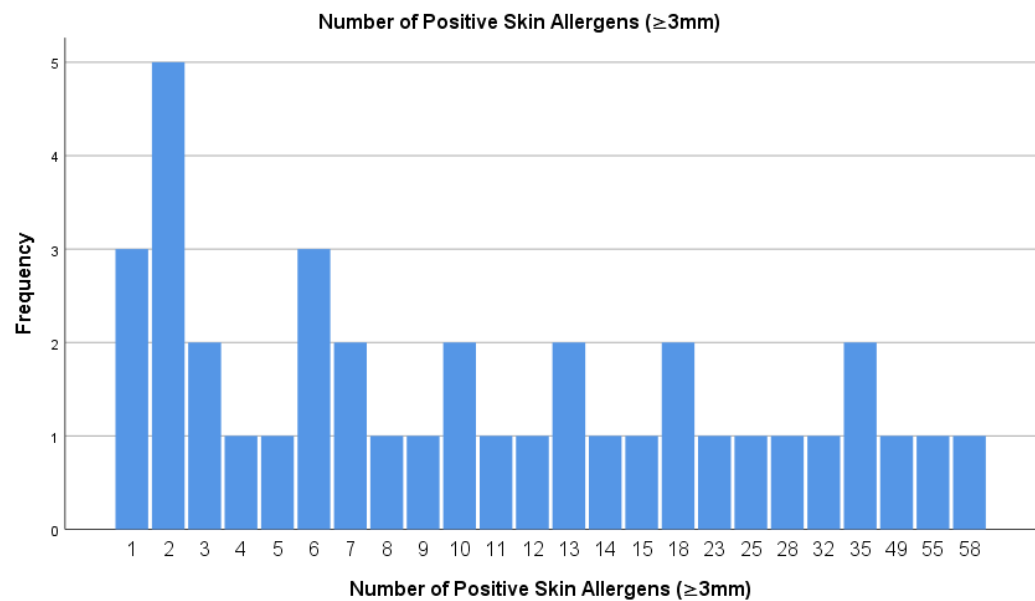


Table 4: Demographic data and summary of ImmunoCap test and skin prick test results of 44 patients who received omalizumab therapy.

Description	Result
Total number of patients who got omalizumab therapy	N=44
Positive ImmunoCap test patients	n=26
Positive Skin prick test patients	n=11
Negative Immunocap test patients	7
Gender	11 males, 33 females
Mean Age	56.2years (Range: 23 to 81years)
Mean total IgE	373.2KU/L
Patients with baseline FEV ₁ ≥80% predicted	11
Patients with FEV ₁ ≥80% predicted after at least 6 months of omalizumab therapy	18
Patients with baseline Asthma Control Test (ACT) score≥19	2
Patients with Asthma Control Test (ACT) score≥19 after at least 6 months omalizumab therapy	10

Table 5: Investigation results of 7 patients who received omalizumab based on elevated total IgE result alone.

Patient	Positive Skin prick results	Positive ImmunoCap results	Total IgE (KU/L)
1	N/A	o	87
2	N/A	o	105
3	N/A	o	155
4	N/A	o	164
5	N/A	o	503
6	o	o	519
7	N/A	o	751
Mean total IgE of the patients = 319KU/L			

Tables 4 and 5 describe the characteristics of the patients on omalizumab. There were 44 patients on omalizumab with a mean age of 56 years (range: 23-81 years). 16% of patients in the cohort on omalizumab therapy had a negative ImmunoCap test but elevated IgE level, with a mean of 319 KU/L. 59% had a positive ImmunoCap test and the remaining 25% had positive SPT.

The mean total IgE level of the omalizumab cohort was 373 KU/L, which was not very different from the mean total IgE of all the patients with a positive ImmunoCap test. 11 (25%) patients had an FEV₁ equal or greater than 80% before omalizumab therapy and 2 (4.5%) patients had a baseline ACT score $\geq$ 19 before omalizumab.

Table 6: Comparison of patients' mean FEV₁ before omalizumab therapy and while on therapy for at least 6 months.

Description	Before omalizumab therapy	After omalizumab therapy
Mean FEV ₁ (standard deviation)	1.99 (0.69)	2.06 (0.83)
Difference in mean	0.07	
t-score (from paired t-test)	-1.72	
95% Confidence interval	-0.17 to 0.02	
P-value	0.097 (not significant)	
Number of patients with complete data: 26		

Table 7: Comparison of patients' mean % predicted FEV₁ before omalizumab therapy and while on therapy for at least 6 months.

Description	Before omalizumab therapy	After omalizumab therapy
Mean % Predicted FEV ₁ (standard deviation)	74.50 (17.32)	77.46 (20.59)
Difference in mean	2.96	
t-score (from paired t-test)	-1.66	
95% Confidence interval	-6.63 to 0.70	
P-value	0.109 (not significant)	
Number of patients with complete data: 26		

Tables 6 and 7 give the results of the paired T-test, showing no significant difference between the mean baseline FEV₁ and mean

baseline % predicted FEV₁ when comparing mean results after at least 6 months of omalizumab therapy.

Table 8: Comparison of patients' mean ACT (asthma control test) score before omalizumab therapy and while on therapy for at least 6 months.

Description	Before omalizumab therapy	After omalizumab therapy
Mean ACT score (standard deviation)	11.92 (3.90)	14.13 (5.23)
Difference in mean	2.21	
t-score (from paired t-test)	-2.24	
95% Confidence interval	-4.21 to -0.21	
P-value	0.031 (significant)	
Number of patients with complete data: 38		

Table 8 shows a significant increase from the mean baseline ACT when compared with the ACT score after at least 6 months of omalizumab.

Discussion

According to the American Academy of Allergy, Asthma, and Immunology, allergic asthma is the most common type of asthma and accounts for the largest share of an estimated \$50.3 billion spent yearly in the USA on the management of asthma. The diagnosis of allergic asthma involves a test of serum total IgE alongside a sensitization test to specific allergens either by ImmunoCap or SPT. Unlike in children, atopic asthma is not the most common phenotype in adults. Atopic asthma accounts for 34% of the severe asthmatic phenotype whereby persistent eosinophilic airway inflammation constitutes 52% [13]. The obesity-related phenotype is also commonly seen in adults, mostly female, and is associated with frequent symptoms [14].

In this study, the diagnosis of allergic asthma requires the presence of allergic-

related symptoms such as rhinitis or other atopic symptoms, seasonal variability in symptoms, and an elevated total IgE level greater than 100 KU/L with or without the presence of ImmunoCap or SPT. The presence of elevated total IgE has been shown to correlate closely with asthma prevalence [15], independent of the serum-specific antibody [7]. The ImmunoCap tests were performed at LabCorp and Quest diagnostic laboratory and a minimum level of 0.35 KU/L was required to be classified as positive. SPT was performed in our office with adherence to the SPT practice parameter [16]. The ImmunoCap test provides a similar result as that obtained with SPT, except in the diagnosis of aeroallergens where it suffers from slightly lower sensitivity [17,18]. The intradermal method was not utilized in any of the allergy skin tests; this method is known to have a higher sensitivity than SPT but it suffers from a high rate of false-positive reactions. A study by Brown et al. also reported an absence of correlation between positive intradermal reactions with either clinical or immunologic evidence of allergy in patients with negative SPT [19]. In this

study, 57% of adult allergic asthma patients had a positive sensitization test to specific allergens. ImmunoCap testing was predominantly used with only 10% of the patients tested by SPT. The low utilization of SPT in our practice could have falsely reduced the percentage of patients classified as having allergic asthma with negative ImmunoCap tests [17]. The mean total IgE of the patients with a positive ImmunoCap test is higher than with those with negative ImmunoCap results. The correlation of total IgE with ImmunoCap is significant ($p < 0.0001$) and with moderate strength ($r = 0.36$). Of the patients who are ImmunoCap-negative but have elevated total IgE ≥ 110 KU/L, 42% have typical allergic symptoms. There is a possibility that some of the negative ImmunoCap group could have tested positive for SPT. Erwin et al. compared the levels of total IgE and specific IgE to dust and cats in children in New Zealand and Sweden, respectively, and found a significant correlation with dust mites and not with cats [20]. Gusareva et al. performed a similar study in Siberia and did not find any correlation between total IgE and dust mites but a significant correlation was noted with birch, dog, and cat allergens in patients with total IgE ≥ 200 KU/L [21]. Our study also supported the idea that elevated IgE levels, in the right clinical setting, are more important than sensitization to allergens for the diagnosis of allergic asthma [22]. In the cohort of 44 patients undergoing omalizumab therapy for at least six months, the average IgE was 373 Ku/L, which was not very different than the average for all patients in the ImmunoCap-positive group. The patients on omalizumab have severe persistent asthma, as defined by the GINA guidelines

[23]. Six patients without evidence of allergen sensitization by ImmunoCap testing and one patient with negative allergen sensitization to both SPT and ImmunoCap have, collectively, an average total IgE of 319 KU/L. All the patients in this omalizumab cohort have been undergoing treatment for more than six months and were all considered to be doing well, with an improvement in their symptoms and a decrease in the frequency of asthma exacerbation, as judged by their treating pulmonologists. The exact impact on exacerbation reduction is not able to be proven objectively due to the retrospective nature of the study. Omalizumab has been shown in many studies to reduce asthma exacerbation [24,25] and give the improved quality of life as measured by the Asthma Quality of Life Questionnaire (AQLQ[S]) [26]. The ACT score improved significantly in the patients receiving omalizumab therapy, but we did not see any significant improvement in their FEV₁. In a similar, real-world experience study performed by Tzortzaki et al., there was an improvement in the ACT score but, unlike our study, there was also an improvement in FEV₁ among patients on omalizumab [27]. The seven patients who received omalizumab therapy despite negative allergen sensitization testing also benefited from the treatment, with an improvement in their symptoms and ACT scores as judged by their treating physicians. The benefit of omalizumab therapy cannot be predicted from the pre-treatment level of specific IgE [28]. In addition, the benefit of omalizumab has been demonstrated in a group with non-atopic asthma [29]. In this real-world study, we describe the characteristics of patients diagnosed with allergic asthma and confirmed findings

from other studies that females are the predominant patients and that total IgE level correlates more closely with allergic asthma prevalence than the serum specific IgE. We also confirm the benefit of omalizumab in a small cohort by showing an improvement in symptoms and ACT scores. The possible utility of omalizumab in non-atopic asthma patients was also suggested by our data, demonstrating the beneficial effect of omalizumab in the seven patients included in the analysis who tested negative in the allergen sensitization

test; however, the small size of our omalizumab cohort and the retrospective nature of the study weaken the significance of our findings. Furthermore, the study was conducted at a single-specialty pulmonary practice and the findings may not apply to all patients with allergic asthma. The generalizability of the study is limited by the fact that we only evaluated asthmatic patients with elevated total IgE levels and did not include allergic asthma patients that may have normal total IgE levels.

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