

Clinically Significant Variability of Serum IgE Concentrations in Patients with Severe Asthma

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Objective. To determine the magnitude of immunoglobulin E (IgE) variability in a cohort of patients with severe asthma considered for omalizumab therapy. **Methods.** Retrospective chart review identified 65 patients with two or more IgE determinations out of the 124 patients referred to the Cleveland Clinic Respiratory Institute for treatment with omalizumab from 2003 to 2011. Patients with conditions known to affect IgE concentrations were excluded. Demographic data, pulmonary function testing, medications, smoking status, and atopy were recorded. The range of variability and percent variability in relation to baseline serum IgE were calculated. **Results.** The median difference of serum IgE between the minimal and maximal values was 94.9 IU/ml (IQR 26.3–324.1 IU/ml). Percent variability from minimum value had a median of 75.5% (IQR 23.3–152.6%). There was no correlation between age, body mass index, lung function, and IgE variability. Greater variability was associated with female gender ($p = .06$). There was no association with peripheral eosinophilia, systemic corticosteroid use, and leukotriene modifier use at presentation. The observed variability would have affected omalizumab dosing in 20 out of 42 patients. Six patients who may have qualified at different time points would not have been deemed candidates based on an IgE concentration <30 IU/ml or >700 IU/ml. **Conclusion.** Serum IgE concentration may have clinically significant variability over time, affecting candidacy and dosing of omalizumab. Our findings imply that repeating serum IgE determinations merits consideration for patients whose initial concentrations are <30 or >700 IU/ml. Prospective studies are warranted to delineate the factors that contribute to IgE variability.

Keywords immunoglobulin E, omalizumab, severe asthma, variability of IgE

INTRODUCTION

Asthma is a syndrome characterized by airway inflammation, airflow obstruction, and airway hyperreactivity. It is well recognized that airway inflammation is the root cause of asthma pathogenesis (1). In most patients with asthma, the inflammation is mediated by immunoglobulin E (IgE) antibody, which serves this role via sensitization of mast cells and basophils. Epidemiologic evidence indicates that a direct correlation exists between serum IgE concentration and asthma prevalence (2), airway hyperreactivity (3), and poor lung function (4, 5). Omalizumab is a humanized monoclonal antibody against the IgE molecule (6). Parenteral administration of the drug results in the formation of multimeric IgE–drug complexes, which inhibit binding with IgE receptors on effector cell surfaces. As a consequence, the early- and late-phase asthmatic responses to antigen are reduced without abrogation (7–9). Clinical trials with omalizumab involving patients with severe asthma demonstrated reduction in use of other anti-inflammatory therapy, reduction in the use of rescue medications for asthma, reduction in asthma exacerbations requiring oral corticosteroids, and improvement in asthma quality-of-life indices (10, 11). The drug is recommended for use in the treatment of properly selected patients with

poorly controlled severe persistent asthma in the third expert panel report of the National Asthma Education and Prevention Program (12).

Omalizumab dosing is based on pretreatment serum IgE concentration and body weight. The maximum allowed serum IgE concentration is 700 IU/ml. The drug is not recommended when the serum IgE concentration is less than 30 IU/ml. In the presence of limited data on the variability of serum IgE over time, we hypothesized that clinically significant variability in serial concentrations of IgE may exist that could affect candidacy for anti-IgE therapy.

METHODS

We performed a retrospective chart review of all patients evaluated for treatment with omalizumab at our main campus from July 2003 to April 2011. Among 124 patients who were evaluated, 65 patients who had two or more IgE determinations over time were included in our analysis. Patients who had concomitant diseases or conditions that are known to affect serum IgE concentrations were excluded. These included atopic dermatitis ($n = 7$), stryngyloidiasis ($n = 1$), suspected or proven allergic bronchopulmonary aspergillosis ($n = 3$), eosinophilic pneumonia ($n = 4$), drug reaction with eczema ($n = 1$), ongoing immunotherapy ($n = 2$), and continuing treatment with omalizumab ($n = 4$). One patient was excluded as the

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assay used to determine serum IgE could not be verified. Quantification of serum IgE concentrations was performed with ImmunoCAP Total IgE (Phadia AB, Uppsala, Sweden) and STAIA-PACK IGEII (TOSOH Medics, Inc., South San Francisco, CA, USA). The two methods have excellent correlation ($r = 0.98$, slope = 1.03) and identical reference ranges.

Age, race/ethnicity, body mass index, smoking status, presence of atopy, spirometric variables (forced expiratory volume in 1 second in liters (FEV₁), mean forced expiratory flow between the 25th and 75th percentile of forced vital capacity (FEF₂₅₋₇₅), and peak expiratory flow), presence of eosinophilia, and medications (systemic corticosteroids, inhaled corticosteroids, long-acting beta-2 agonists, leukotriene modifiers, and short-acting beta-2 agonist) were recorded.

Variability in IgE was calculated as the difference between the maximum and minimum determination of IgE expressed as a percentage of the minimum value ($\text{IgE max} - \text{IgE min} / \text{IgE min} \times 100$).

Assessment of clinical significance was carried out by evaluating the dose of omalizumab that would be prescribed for each IgE determination, and whether any values were outside the range of FDA approved IgE concentrations, that is, <30 IU/ml and >700 IU/ml. Affected patients were recorded if they would have required a dose adjustment or would not have received the drug due to restrictions based on serum IgE concentration determination at any given time point.

Statistical Analysis

The variability in IgE concentrations was expressed as median, interquartile range (IQR), and mean $\pm$ standard deviation. The association between variability and continuous variables (age, body mass index, FEV₁ (percent predicted), FEF₂₅₋₇₅ (percent predicted), peak expiratory flow (percent predicted)) was assessed using Spearman correlation coefficient. Wilcoxon rank sum test was used to assess the association between variability and categorical variables (gender, race, presence of eosinophilia, systemic corticosteroid use, and leukotriene modifier use).

RESULTS

Medical records of 42 patients who were considered for omalizumab administration and had two or more IgE determinations over a period of 2.3 ± 2.2 years were evaluated. The clinical characteristics of the patients are displayed in Table 1. The mean age was 45.6 ± 13.7 years. Thirty-one patients were female. Twenty-six patients were Caucasian and 15 were African American.

IgE Variability

In our cohort, the difference between the maximum and minimum IgE concentration (i.e., range) had a median value of 94.9 IU/ml (IQR 26.3–324.1 IU/ml, mean 324.7 ± 551.1 IU/ml). Variability between the maximum and minimum IgE value had a median value of 75.5%

TABLE 1.—Baseline characteristics of the patients ($n = 42$).

Clinical variable	Measurement
Age (years) (mean $\pm$ SD)	45.6 $\pm$ 13.7
Female sex [n /total no. (%)]	31/42 (73.8%)
Body mass index ^a (kg/m ²) (mean $\pm$ SD)	32.0 $\pm$ 6.6
Active smoking status [n /total no. (%)] ^b	6/42 (14.2%)
Presence of atopy [n /total no. (%)] ^c	36/42 (85.7%)
Eosinophilia [n /total no. (%)] ^d	12/35 (34.2%)
FEV ₁ percent predicted (%) (mean $\pm$ SD)	65.1 $\pm$ 21.2%
FEF ₂₅₋₇₅ percent predicted (%) (mean $\pm$ SD)	40.0 $\pm$ 23.1%
PEF percent predicted (%) (mean $\pm$ SD)	73.9 $\pm$ 27.5%
Systemic corticosteroid regimen [n /total no. (%)] ^e	27/40 (67.5%)

^aThe body mass index is the weight in kilograms divided by the square of the height in meters.

FEV₁, forced expiratory volume in 1 second in liters; FEF₂₅₋₇₅, mean forced expiratory flow between the 25th and 75th percentile of forced vital capacity; PEF, peak expiratory flow (l/s).

^bActive smoking status was defined as smoking a cigarette during the past 30 days.

^cAtopy has been defined as the presence of a positive skin test or a positive RAST on chart review.

^dEosinophilia was defined as the absolute eosinophil count >450 cells/ μ l. Data were missing in seven patients.

^ePatients on oral/intramuscular/intravenous corticosteroids on the day or 2 weeks prior to the day of initial total IgE determination. Datum was missing in one patient.

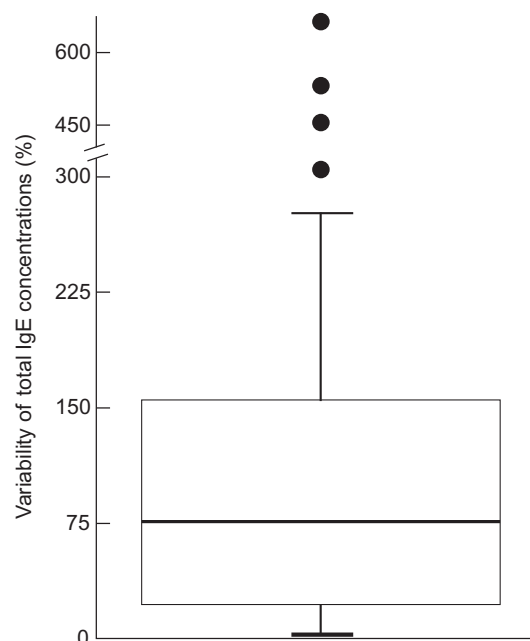


FIGURE 1.—Variability of serum IgE in all study subjects. Whiskers extend to 1.5 times the interquartile range above and below the 75th and 25th percentile. Outliers are represented by dots.

(IQR 23.3–152.6%, mean $118.3 \pm 145.5\%$, Figure 1). The cohort was stratified into two groups comprising patients with IgE concentrations <1000 IU/ml (Figure 2a) and patients with IgE concentrations >1000 IU/ml (Figure 2b) for improved visualization of observed variability.

Association between IgE Variability and Categorical Variables

As shown in Table 2, females tended to have greater variability compared with males (median value of 81.7% vs. 27.4%, $p = .06$). IgE variability was greater among African Americans compared with that among

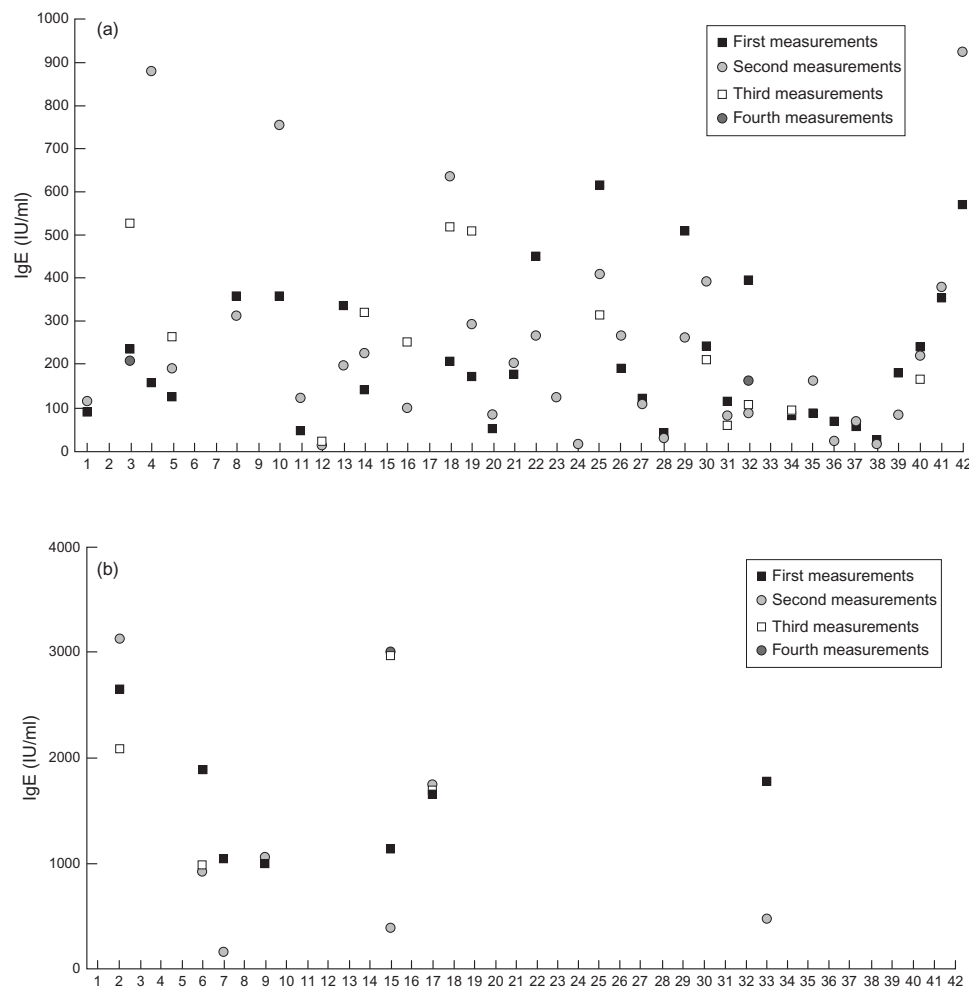


FIGURE 2.—(a) Scatter plot showing variability of serial serum IgE determinations in individual patients (IgE concentrations <1000 IU/ml). Consecutive measurements are denoted by different symbols. (b) Scatter plot showing variability of serial serum IgE determinations in individual patients (IgE concentrations >1000 IU/ml). Consecutive measurements are denoted by different symbols.

Caucasians, but this did not reach statistical significance (median value of 112% vs. 67.4%, $p = .11$). Presence of eosinophilia, use of systemic corticosteroids and leukotriene modifiers at the first visit were not significantly associated with IgE variability.

Association between IgE Variability and Continuous Variables

There was no significant correlation between variability of IgE concentrations over time and age ($r = 0.09$, $p = .57$), body mass index ($r = -0.15$, $p = .35$), FEV₁ predicted ($r = -0.18$, $p = .28$), peak expiratory flow percent predicted ($r = -0.23$, $p = .17$) (Table 3).

Assessment of Clinical Significance

A total of 20 out of the 42 patients would have required a dose adjustment based on serum IgE determinations at different time points. A total of 6 out of the 42 patients who may have qualified at different time points would not have been deemed candidates for anti-IgE therapy based on an IgE serum concentration <30 IU/ml or >700 IU/ml. One patient would have been excluded due to a low IgE

concentration, while the rest would have been excluded due to an elevated IgE concentration.

DISCUSSION

Based upon high-quality evidence from randomized, placebo-controlled trials (10, 11), omalizumab is an efficacious therapeutic intervention for patients with poorly controlled severe persistent allergic asthma in step 5 or step 6 of the EPR-3 guidelines. Dosing of omalizumab is dependent on body weight and serum IgE concentration. There are no previously published studies to our knowledge which have directly assessed the degree of longitudinal variation in serum IgE that could influence eligibility for or dosing of anti-IgE therapy in individuals with severe persistent allergic asthma.

We performed a retrospective review of medical records of 124 patients who were evaluated in the Respiratory Institute of the Cleveland Clinic for consideration for omalizumab therapy. In 42 patients who had two or more serum IgE determinations, and who did not have co-morbid conditions that may affect IgE

TABLE 2.—Association between percent variability of IgE and baseline characteristics.

Variable	n	Variability of serum IgE median (IQR) ^a	P-value ^b
Gender			.06
Male	11	27.4 (5.9–93.5)	
Female	31	81.7 (39.8–162.4)	
Race ^c			.11
Caucasian	26	67.4 (15.1–108.6)	
African American	15	112.0 (39.8–205.2)	
Eosinophilia			.18
Present	12	87.3 (63.7–130.6)	
Absent	23	49.7 (15.1–128.5)	
Systemic corticosteroids			.61
Yes	27	65.6 (18.8–152.6)	
No	13	81.7 (49.7–159.4)	
Leukotriene modifiers			.47
Yes	32	81.4 (30.4–161.6)	
No	7	69.0 (7.04–117.5)	

^aInterquartile range.^bWilcoxon rank sum test was used to assess the association between categorical variables and the percent variability of serum IgE.^cDatum was missing in one patient.

TABLE 3.—Association between variability of IgE and baseline characteristics.

Clinical variable	Spearman correlation coefficient	P-value
Age	0.09	.57
BMI	−0.15	.35
FEV ₁ % predicted	−0.18	.28
PEF % predicted	−0.16	.32
FEF _{25–75} % predicted	−0.24	.14

BMI, body mass index; FEV₁, forced expiratory volume in 1 second in liters; PEF, peak expiratory flow; FEF_{25–75}, mean forced expiratory flow between the 25th and 75th percentile of forced vital capacity.

concentrations, we found a significant variability in IgE concentrations over time. The observed variation over time in serum IgE concentrations is a clinically significant finding that has implications for management of patients with poorly controlled severe persistent allergic asthma, who are judged to be potential candidates for anti-IgE therapy. Our data suggest that for such patients whose initial serum IgE concentration is either less than 30 IU/ml or exceeds 700 IU/ml, a repeat determination of IgE may be warranted. Our data do not allow us to recommend a specific time frame for rechecking of serum IgE. The erratic and unpredictable pattern of serum IgE over time that we observed in our cohort also suggests that for patients who are receiving omalizumab at low or moderate dose without improvement, a determination of free IgE may be obtained to assess the possibility that a higher dose may be required to achieve a salutary response to anti-IgE therapy.

The methodologies used to determine serum IgE concentration (STAIA-PACK IGEII and ImmunoCAP) had excellent correlation ($r = 0.98$). The values obtained in our clinical laboratory had identical reference ranges (slope = 1.03). Moreover, when paired measurements that utilized the same test were assessed, similar

variability of serum IgE was observed with either test (data not shown). This strongly suggests that the test that was employed to determine serum IgE did not impact the findings of the study.

Serum IgE concentrations may be affected by age, use of corticosteroids, and seasonal changes. However, the variability observed in our patients was not associated with these factors.

Serum IgE concentration may vary with age. Progressive increase in total IgE concentrations has been reported in a large birth cohort during the first 10 years of life regardless of the atopy status (13). In the TENOR cohort which was a prospective, observational study of patients with severe or difficult to treat asthma, the mean value of total IgE concentrations was 88 IU/ml (14). The mean of total IgE concentrations had a bimodal peak in males (ages 11–15 and 31–35 years) and a unimodal peak in females (ages 11–15 years) (14). Mean IgE concentrations declined only modestly after age of 41–45 years (14). The mean age of patients in our study was 45 years. The mean time interval between IgE determinations in our patients was approximately 2 years. When greater than 10% change was taken as a threshold, 17 patients had an upward trend, 19 had a downward trend, and 6 had no significant change over the course of IgE determinations. Therefore, we do not believe age-related changes in serum IgE concentration would have a significant impact on our findings.

The effect of corticosteroid use on IgE concentrations has been the subject of various reports. High-dose corticosteroid therapy has been reported to reduce serum IgE concentrations (15). However, Posey et al. (16) reported serum IgE concentrations to be dramatically increased after a week of corticosteroids in a study of 21 nonsteroid-dependent asthmatics. Similarly, asthmatic patients displayed higher serum IgE concentrations after 1 week of treatment with oral prednisone (17). Moreover, hydrocortisone increases in vitro total and allergen-specific IgE production by peripheral blood mononuclear cells from atopic subjects (18). In our cohort, 27 patients received systemic corticosteroids in a 14-day period prior to IgE determination. The magnitude of variability was not significantly different between patients who received corticosteroids as part of their asthma regimen on initial presentation and those who did not. Consequently, it is unlikely that the observed variability would be explained on the basis of corticosteroid use.

Another factor that may influence IgE concentrations is immunotherapy. An increase of total IgE and specific IgE concentrations during immunotherapy (19–21) as well as no significant difference have been reported (22, 23). The magnitude of change may be modest (24) and concentrations tend to return to normal at the end of treatment. Nevertheless, we chose to exclude those patients who were undergoing immunotherapy during the IgE determinations.

Seasonal changes in allergen exposure may also induce rise in specific IgE toward the allergen. In a study of 17 asthmatics, total and specific IgE concentrations increased

during the pollen season. The change was large enough in magnitude to warrant adjustment of omalizumab dosing in five of these patients (25). When we grouped patients into those who had their IgE concentration determined during the same or consecutive month of the year ($n = 17$) and those whose testing was farther apart in the year ($n = 25$), we did not find a significant difference in variability ($p = .75$, data not shown). While not definitive, this analysis indicates there were factors in addition to seasonal variation in serum IgE that contributed to the variability in our cohort.

CONCLUSION

Serum IgE is an important variable for prescribing anti-IgE therapy. We report clinically significant intra-subject variability in serum IgE measurements in patients with severe persistent asthma who were deemed potential candidates for anti-IgE therapy. Nearly half of our study patients would have required dose adjustment and one in seven would not have received anti-IgE treatment, had they been tested at different times. However, one must be careful in extrapolating our incidence data to a general population. The cohort reported in this study represents a highly selected group of individuals referred to a tertiary care center for the treatment of severe asthma. Although we could not identify any specific reasons for repeating IgE concentrations during our chart review, we speculate that this may be an additional marker for particularly difficult to manage asthma patients. We also suggest that factors other than seasonal allergen burden, age, immunotherapy, or corticosteroids may be responsible for observed changes. Further study is required to achieve a better understanding of these factors and to assess the incidence of serum IgE variability in a community population of patients with severe persistent asthma.

DECLARATION OF INTEREST

The authors have seen and agreed with the contents of the Manuscript. The authors affirm that no funding agreement limited our ability to complete and publish our research/study. The authors had complete control of primary data. Dr. Hatipoglu reported being the recipient of an Investigator Initiated Research Grant from Novartis. Dr. Lang reported the following conflicts of interest:

Genentech/Novartis: Research support, honoraria for speaking; Merck: Research support, consulting, and honoraria for speaking; Sanofi-Aventis: Consulting; Teva: Honoraria for speaking; GlaxoSmithKline: Honoraria for speaking; Hycor: Consulting.

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