Serum total IgE levels and total eosinophil counts: relationship with treatment response in patients with acute asthma*, **

Relação dos níveis séricos de IgE total e das contagens de eosinófilos com a resposta ao tratamento em pacientes com asma aguda

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Abstract

Objective: To determine whether serum total IgE levels and total eosinophil counts have any relationship with the response to routine pharmacological treatment in patients with acute asthma. **Methods:** A cross-sectional study involving 162 patients with acute asthma. Serum total IgE levels, peripheral blood cell counts and eosinophil counts were determined. The treatment was adjusted for each patient according to the severity of asthma. Spirometry was performed at baseline and two weeks after the treatment. The patients were divided into two groups: high IgE (≥100 IU/mL) and low IgE (<100 IU/mL). We compared the two groups in terms of the relationships between baseline values and final values (percentage change) for the following parameters: FEV_1, FVC, $FEF_{25-75\%}$, peripheral white blood cell counts and eosinophil counts. **Results:** There were no significant differences between the groups regarding the percentage changes of the studied parameters. Nor were there significant differences between the groups regarding FEV_1, FVC, and $FEF_{25-75\%}$ (% of the predicted values) at baseline. **Conclusions:** On the basis of these findings, we conclude that serum total IgE levels, peripheral white blood cell counts and eosinophil counts cannot predict the response to the pharmacological treatment of patients with acute asthma.

Keywords: Asthma/drug therapy; Eosinophils; Immunoglobulin E

Resumo

Objetivo: Determinar se há uma relação dos níveis de IgE total no soro e das contagens de eosinófilos com a resposta à farmacoterapia de rotina em pacientes com asma aguda. **Métodos:** Estudo transversal com 162 pacientes com asma aguda. Foram determinados os níveis séricos de IgE total, as contagens de células no sangue periférico e as contagens de eosinófilos. O tratamento foi ajustado individualmente de acordo com a gravidade da asma. Foi realizada espirometria antes do início do tratamento e duas semanas após seu término. Os pacientes foram divididos em dois grupos: alto nível de IgE (≥ 100 UI/mL) e baixo nível de IgE (< 100 UI/mL). Foram comparadas entre os dois grupos as relações das determinações basais e das alterações em percentual dos seguintes parâmetros: VEF, CVF, $FEF_{25-75\%}$, contagem de células brancas no sangue periférico e contagem de eosinófilos. **Resultados:** Não houve diferenças significativas entre os grupos em relação às alterações em percentual dos parâmetros estudados. Tampouco houve diferenças significativas entre os grupos em relação aos valores basais de VEF, CVF e $FEF_{25-75\%}$, em % do predito. **Conclusões:** Com base nesses achados, concluímos que os níveis séricos de IgE total, as contagens de células brancas no sangue periférico e as contagens de eosinófilos não são preditores do tratamento farmacológico de pacientes com asma aguda.

Descritores: Asma/quimioterapia; Eosinófilos; Imunoglobulina E.

Introduction

Asthma is a condition characterized by variable airflow obstruction, fluctuation of symptoms and changes in the level of bronchial responsiveness, as well as in the degree of airway inflammation. An elevation in serum IgE levels, a marker of allergic inflammation and atopy, contributes to asthma and is considered a potent predictor of the development of asthma. In one study, the increase in the provocative concentration causing a 20% fall in FEV_1 (PC_{20}) after the administration of inhaled corticosteroids was greater in patients with elevated IgE levels than in those with lower IgE levels.[1] It has recently been reported that high IgE levels lower the

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probability of hospitalization during an asthma attack in children.[2] It is unknown whether asthma patients who do not respond well to one medication might respond to another.

In children with mild-to-moderate persistent asthma, a favorable response to inhaled corticosteroids was associated with higher total eosinophil counts, as well as with higher levels of exhaled nitric oxide, of serum IgE and of other markers of allergic inflammation.[3] In addition, in a study involving patients with stable mild-to-moderate asthma who were treated with montelukast for four weeks, the authors concluded that there was no significant correlation between the clinical response and serum IgE levels.[4] In the general population, the percentage of patients with asthma and airway responsiveness is greater among those with high IgE levels than among those with low IgE levels.[5]

Another group of authors concluded that IgE facilitated the development of bronchial responsiveness in patients with asthma.[5] In the absence of parasitic infections, increased serum total IgE is considered as a hallmark of allergy. One study showed that pulmonary responses to inhaled corticosteroids in adults with mild-to-moderate persistent asthma are associated with specific characteristics of the patients and with markers of airway inflammation.[6]

The purpose of this study was to determine whether there is a relationship between serum total IgE levels and the short-term clinical response to pharmacological treatment in adults who require medication for the management of acute asthma.

Methods

The study involved adult patients treated for acute asthma at a private clinic between March of 2004 and February of 2006, during a two-week follow-up period. The treatment was adjusted for each patient according to the severity of the disease.[7] Prior to the treatment, serum total IgE levels, peripheral white blood cell counts and eosinophil counts/percentages were determined. Spirometry was performed at baseline and two weeks after the treatment using a spirometer (ST-95; Fukuda Sangyo Inc., Antipolo City, The Philippines). The primary outcome measure was the percentage change between FEV_1 at baseline and that two weeks after the treatment. The subjects included were adult asthma outpatients (FEV_1 = 50-85% of the predicted) who completed the two-week treatment. The diagnosis of asthma was made based on clinical grounds and required objective criteria of reversible airway obstruction—an improvement in $FEV_1 \geq 12\%$ (and ≥ 200 mL) after the inhalation of a short-acting β_2-agonist—as defined by the American Thoracic Society.[8] Serum total IgE levels (IU/mL) were determined using an immunoassay system (Monobind Inc., Costa Mesa, CA, USA). Serum total IgE levels, white blood cell counts and eosinophil counts were determined in the Dr. Ehteram Laboratory Services Center. Informed consent was obtained from all the participants prior to the beginning of the study. Serum total IgE levels ≥ 100 IU/mL were defined as high, since levels above this value have been associated with sensitization and subsequent risk of asthma.[9]

The results of pulmonary function tests were calculated as percentage of change relative to baseline FEV_1 using the following equation:

$$\text{Percentage of change} = [(\text{observed} - \text{base}) / \text{base}] \times 100$$

where *observed* is the post-treatment value and *base* is the baseline value on the day prior to the treatment.

Table 1 - Clinical characteristics of the studied patients.[a]

Characteristic	Result
Gender	
Male, n (%)	90 (55.6)
Female, n (%)	72 (44.4)
Age, years	36.4 ± 13.5
Serum total IgE, IU/mL	241.30 ± 200.45
Serum total IgE ≥ 100 IU/mL	325.2 ± 186.9
Serum total IgE < 100 IU/mL	53.3 ± 26.7
White blood cells/mL	39,590.3 ± 2,982.9
Peripheral blood eosinophils, %	2.87 ± 2.57
Peripheral blood eosinophils/mm^3	268.5 ± 254.8
FEV_1, L	1.73 ± 0.61
FEV_1, % predicted	54.08 ± 14.07
FVC, L	2.60 ± 0.82
FVC, % predicted	69.26 ± 15.52

[a]Results expressed as mean ± SD, except where otherwise indicated.

Table 2 - Results of pulmonary function tests before and after the treatment in acute asthma patients.[a]

Parameter	Before treatment	After treatment	p
FVC, L	2.60 ± 0.82	3.53 ± 0.89	< 0.001
FVC, % of predicted	69.26 ± 15.52	93.87 ± 14.56	< 0.001
FEV_1, L	1.73 ± 0.61	2.66 ± 0.74	< 0.001
FEV_1, % of predicted	54.08 ± 14.07	83.39 ± 16.12	< 0.001
$FEF_{25-75\%}$, L/s	1.12 ± 0.55	2.21 ± 0.98	< 0.001
$FEF_{25-75\%}$, % of predicted	27.23 ± 11.87	54.38 ± 20.97	< 0.001

[a]Results expressed as mean ± SD.

Statistical analysis

Data are expressed as mean ± SD. The Kolmogorov-Smirnov test was used for the distribution of quantitative variables. Mean ± SD values of pulmonary function tests (FEV_1 and FVC) prior to and after the treatment were calculated, and p values were compared by means of Student's t-test for paired and unpaired data. Comparisons between the groups were evaluated using the Mann-Whitney U-test or the Wilcoxon signed-rank test, when appropriate. Values of $p \leq 0.05$ were considered significant. Statistical analyses were performed using the Statistical Package for the Social Sciences, version 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

The study involved 162 asthma patients (90 males and 72 females; mean age of 38.0 ± 14.4 and 34.4 ± 12.0 years; respectively). The baseline characteristics of the patients are presented in Table 1.

Table 2 summarizes the results of pulmonary function tests before and after treatment. As shown in Table 2, there were significant differences between the mean pre-treatment and post-treatment values of FEV_1, FVC and $FEF_{25-75\%}$ ($p < 0.001$ for all).

As can be seen in Table 3, there were no statistically significant differences between the patients with high serum total IgE and those with low serum total IgE in terms of the baseline values of FEV_1, FVC, and $FEF_{25-75\%}$ ($p = 0.79$, $p = 0.69$ and $p = 0.45$, respectively), or in terms of the percentage changes of FEV_1, FVC, $FEF_{25-75\%}$, peripheral white blood cell counts and eosinophil counts.

Discussion

The results of the present study indicate that, in acute asthma patients who are under treatment, serum total IgE levels are not associated with the percentage changes in spirometric values, peripheral white blood cell counts or eosinophil counts. According to the current

Table 3 - Comparison between acute asthma patients with high or low IgE levels regarding pulmonary function parameters, peripheral white blood cell counts and eosinophil counts.[a]

Parameter	High IgE (≥ 100 IU/mL) (n = 112)	Low IgE (< 100 IU/mL) (n = 50)	p
Age, years	35.1 ± 13.5 (32.6-37.7)	39.1.± 13.3 (35.3-42.9)	0.08
Male/Female, n/n	67/45	23/27	
FEV_1, % predicted	53.9 ± 14 (51.3-56.5)	54.5 ± 14.3 (50.5-58.6)	0.79
FVC, % predicted	69.0 ± 15.4 (66.1-71.9)	70.1 ± 15.8 (65.6-74.6)	0.69
$FEF_{25-75\%}$, % predicted	27.7 ± 12.0 (25.4-30.1)	26.2 ± 11.7 (22.8-29.5)	0.45
Δ FEV_1	63.0 ± 13.0 (54.2-72.8)	65.7 ± 58.8 (49.0-82.4)	0.89
Δ FVC	41.8 ± 23.5 (33.6-49.5)	45.2 ± 40.7 (33.7-56.8)	0.74
Δ $FEF_{25-75\%}$	164.7 ± 68.4 (103.3-144.7)	53.3 ± 26.7 (90.7-153.5)	0.68
White blood cells/mm^3	9,532.9 ± 3,015.3 (8,963.1-10,102.7)	9,716.4 ± 2,936.7 (8,881.8-10,551.0)	0.72
Blood eosinophils, %	3.1 ± 2.9 (2.1-3.6)	2.5 ± 1.7 (2.4-3.4)	0.67
Blood eosinophils/mm^3	279.0 ± 272.2 (227.6-330.4)	245.5 ± 212.5(185.1-305.9)	0.72

[a]Results expressed as mean ± SD (95% CI), except where otherwise indicated.

study, the serum total IgE level could not predict the response to the asthma treatment.

Serum total IgE levels have been shown to be associated with various aspects of asthma, including the response to treatment.[3] In the general population, a relationship between serum total IgE levels and airway responsiveness has been reported.[5]

In a study involving subjects with asthma and COPD, serum total IgE was found to be a better independent predictor of changes in PC_{20} throughout the study, more than any other allergic parameters, such as house dust mite-specific IgE, skin tests or blood eosinophil counts.[1] The authors found that higher serum total IgE levels prior to inhaled corticosteroid therapy cause a greater reduction in the degree of nonspecific bronchial responsiveness.[1] The authors concluded that serum total IgE levels cannot accurately be used as a predictor to the response to inhaled corticosteroids in individuals. In contrast to those findings, another group of authors concluded that airway hyperresponsiveness increases over time in non-allergic patients with COPD, and that treatment with an inhaled corticosteroid alone or in combination with oral prednisolone does not alter that increase.[10]

According to epidemiological and immunological studies, it is obvious that IgE plays a central role in the pathogenesis of atopic disease. A number of epidemiological studies have demonstrated a link between circulating levels of IgE and atopic disease. One group of authors showed an association between bronchial hyperresponsiveness to methacholine and serum IgE levels in a population of 1,037 children.[11]

Among children and adults, those with higher IgE levels are more likely to have known asthma or to be diagnosed with the disease in the future.[12] One group of authors also reported that, among non-allergic subjects, asthma is more prevalent in those with elevated IgE levels than in those with normal IgE levels.[13] Previous studies have suggested that elevated serum IgE levels are significantly associated with a higher frequency of symptoms in atopic subjects with asthma or rhinitis.[14,15]

In a longitudinal study, a significant inverse association was found between serum total IgE levels and FEV_1/FVC.[15] The authors suggested that higher IgE levels indicate the presence of a disease process that can involve inflammation or other mechanisms related to IgE production, which can impair lung function over time.[16] Another group of authors concluded that higher serum IgE levels are correlated with lower values of FEV_1, which is related to airway tone, and possibly act via cholinergic mechanisms.[17]

There are no documented reports regarding the effect of serum total IgE levels as a predictor of asthma or its role in the response to asthma treatment. However, the effect that treatment has on serum IgE levels in asthma patients has been reported. In one study, it was shown that a three-month course of inhaled beclomethasone dipropionate (800 μg/day) led to the improvement of the symptoms and a significant reduction in the circulating total and allergen-specific IgE levels in a group of atopic asthma patients.[18] After the administration of corticosteroids, a reduction in IL-4 levels occurs, which results in the reduction of IgE levels. In the current study, the effect of the treatment was evaluated two weeks after its conclusion, because another group of authors reported that there is a significant bronchodilating and bronchoprotective effect after two weeks of active treatment.[19]

Patients with COPD and elevated IgE levels, atopy or sputum eosinophilia form a subgroup of patients with a better prognosis and a greater likelihood of corticosteroid responsiveness.[20] In our patients, we found no statistically significant difference between those with high serum total IgE and those with low serum total IgE in terms of the response to treatment. Among COPD patients, those with features of asthma have a better prognosis than do those with "pure emphysema".[20]

The production of IgE in allergic individuals depends on a series of interactions between B cells, T cells, mast cells and eosinophils, as well as the involvement of different surface molecules and cytokines (IL-4 and IL-13).

Bronchoscopic studies reveal that atopic asthma is characterized by infiltration of the airway wall with eosinophils, mast cells, CD4+ T lymphocytes and cytokines, such as IL-4, and this readily explains why IgE is elevated and can act as a marker of the presence and of the severity of asthma.[21]

In COPD patients, serum total IgE has been shown to be inversely associated with base-

line histamine PC_{20}.[10] In COPD, chronic airway inflammation might also be relevant and possibly more marked in patients with higher IgE levels.

In our study, no statistically significant differences were found between the patients with high and low IgE levels regarding the baseline values of FEV_1, FVC and $FEF_{25-75\%}$. In a study involving adult patients with asthma in Europe, IgE was found to be a strong predictor of moderate-to-severe asthma.[22] In another study, higher total IgE levels were shown to be associated with the degree of asthma severity among younger subjects with difficult-to-treat or severe asthma.[23] Recently, other authors have reported that, among patients with asthma, mean FEV_1 is significantly lower in those with high IgE levels than in those with low IgE levels.[24] Among our patients, baseline FEV_1 was 53.9 ± 14.0% and 54.5±14.3% of predicted, respectively, in those with high and low total serum IgE levels ($p = 0.79$). Unlike the asthma subjects recruited in some other studies, our patients were not in remission.

In the present study, there was no statistical difference between asthma patients with high and low total serum IgE levels in peripheral blood eosinophil counts ($p = 0.72$). In a study, a positive correlation between serum total IgE levels, total blood eosinophil counts and eosinophil cationic protein (ECP) was reported.[25] Eosinophils play an important role in the pathogenesis of asthma. Airway inflammation, involving infiltration of the bronchial wall by activated eosinophils, mast cells and T lymphocytes, is an established feature of asthma. There is considerable evidence that eosinophils also play an important role in bronchial epithelial damage in asthma by releasing cationic proteins. There have been various studies regarding the correlation between eosinophil cationic protein and serum total IgE levels. The most widely examined measures in predicting a response to corticosteroids are airway hyperresponsiveness, exhaled nitric oxide and induced sputum. Of those, sputum eosinophilia has been shown to be the best predictor of a short-term response to corticosteroids.[26] One group of authors reported that baseline values of the clinical parameters used as outcome measures are the major predictors of the clinical response to corticosteroids. The result confirmed that a high percentage of eosinophils in blood or sputum, as a known marker of airway inflammation, adds to this, whereas ECP provides no additional information.[27] The peripheral blood eosinophil count, the serum ECP concentration, and the ECP/eosinophil ratio have been shown to be significantly higher during acute asthma exacerbations than during clinical remission.[28] Other authors reported that a high blood eosinophil count at baseline and an increase in sputum eosinophil count after the reduction of corticosteroids were predictors of loss of asthma control.[29] In yet another study, patients with high sputum eosinophil levels (> 3%) at baseline showed significant improvement in symptoms, pulmonary function and bronchial hyperresponsiveness after treatment, whereas patients with low sputum eosinophil levels showed no significant improvement in most clinical and functional outcomes.[30]

The results presented here indicate that neither serum total IgE levels, peripheral white blood cell counts or eosinophil counts can predict the response to asthma treatment.

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