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Clinical Science

Serum Interleukin-5 Changes in Partly Controlled Atopic Asthmatic Children

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Key words: Interleukin-5 (IL-5); Partly controlled asthma; Inhaled corticosteroids (ICS); Leukotriene modifier (LTA); Atopy.

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Abbreviations: Cys- Lts: Cysteinyl-leukotrienes, FEF: forced expiratory flow, FVC: forced vital capacity, FEV1: forced expiratory volume in the first second, ICS: Inhaled corticosteroids, IL: Interlukin, LTA: Leukotriene modifiers, PEFR: peak expiratory flow rate, PFTs: Pulmonary function tests, Th2: T helper 2 cell.

Abstract

BACKGROUND: Cytokines including Interleukin-5 play a key role in orchestrating the chronic inflammation of asthma. We aimed to determine the level of serum IL-5 in partly controlled atopic asthma in children and to assess the effect of different therapies on their levels.

METHODS: The study included 40 children aged 6-12 years with partly controlled asthma. Cases were randomly divided into two groups; group 'A' receiving Leukotriene modifiers and group 'B' receiving inhaled corticosteroids; each for two months. They were compared to 20 healthy non-asthmatic, matched controls. Serum IL-5 was measured for cases on the first visit and two months after therapy. Absolute eosinophilic count and serum Ig-E were determined. Pulmonary function testing was performed using spirometer at the beginning and two months after regular therapy.

RESULTS: Serum Interleukin-5 was significantly increased in asthmatic children during exacerbation and was significantly decreased after treatment. ROC curve analysis showed significant difference of IgE and PEFR after treatment with leukotriene modifier only.

CONCLUSION: Serum IL-5 seems to have a role in asthma pathogenesis. Efficiency of the two therapies (ICs & LTA) was similar in this group of patients. Both treatments led to significant decline in serum IL-5, IgE levels and eosinophilic count.

Introduction

Asthma is a chronic inflammation of the airways with reversible episodes of obstruction, caused by an increased reaction of the airways to various stimuli [1]. In 2009, Zedan et al [2] found that the prevalence of asthma among school children in the Nile Delta was 7.7 %. GINA guidelines (2011) provide classification of asthma by level of control into three categories (controlled, partly controlled and uncontrolled asthma), based on daytime symptoms, nocturnal symptoms, limitation of activity, need to quick-relief medicine, peak flow rate, and incidence of exacerbation per year [3].

Accumulating evidence indicates that classical Th2 cell derived cytokines (e.g. IL-3, IL-4, IL-5, IL-9, IL-13 and GM-CSF) together with eotaxin play critical roles in the induction of airway hyper reactivity and the development of chronic airway wall remodeling [4]. IL-5 acts as a mediator of activation of eosinophils, influencing adhesion, membrane receptor expression, chemotaxis, and mediator synthesis. Airway eosinophilia has been related to bronchial hyper reactivity, asthma symptoms, and airway narrowing in subjects with asthma [5].

The aim of the present study was to determine the level of serum IL-5 in partly controlled atopic asthma in children during exacerbation and remission of asthma attacks, and to assess its possible role in asthma pathogenesis for these children. We aimed also to compare the therapeutic effect of LTA and ICS in partly controlled asthmatic Egyptian children.

Methods

The study included 40 asthmatic children aged 6-12 years (7.5 ±1.8). They were diagnosed as partly controlled asthma according to GINA Guidelines [3] and were attending chest and allergic out patient clinic of Children's Hospital, Cairo University for receiving treatment in the period from June 2010 to January 2011. Another 20 healthy children of the same age and sex were recruited as controls. All cases had an established clinical history of asthma and positive family history of atopy and were not receiving treatment in the previous month. Patients with history of chronic lung diseases or non-atopic asthmatic children or those presented with stridor were excluded from the study. All the participant's guardians had signed written form consent after explaining the steps and aim of the study to them. Ethical committee of NRC has approved the study.

Complete History

Details about respiratory symptoms (age of onset, duration of asthma, frequency, diurnal variation, precipitating factors, diagnosis, need for oral steroid and frequency of use).

Physical Examination

Anthropometric measurements (height, weight), complete system examination to exclude other diseases, and chest examination to assess respiratory condition were performed. Asthmatic patients were randomly divided into 2 groups, receiving therapy for 2 months:

- Group (A): 20 patients received leukotriene modifiers (Montelukast, 5 mg/day).

- Group (B): 20 patients received inhaled corticosteroids (Fluticasone, 200µg/ day).

Laboratory Investigations

- Total leucocytic count was obtained and the absolute eosinophilic count (AEC) was then calculated from blood smear (Cell/µL).
- Serum Ig-E (IU/ml) was measured by the quantitative Enzyme Linked Imunosorbent Assay (ELISA) (DRG International Inc.USA).
- Serum Interleukin -5 (IL-5):

Two venous blood samples were withdrawn from each child, one sample on the first visit and another sample after two months of regular therapy. Serum IL-5 (for all patients before and after therapy and controls) was determined by the quantitative (ELISA) in accordance with the manufacturer's instructions (IBL International, Germany) and calculated (pg/ml).

Pulmonary Function Tests (PFTs)

PFTs were carried out to all our cases using a spirometer (Fukuda Denshi, Spirosift SP5000) on the second visit when possible or after 2 weeks later. The spirometric parameters included forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), peak expiratory flow rate (PEFR) and forced expiratory flow at 25%-75% (FEF 25-75). All data were presented as percentile of normal values.

Statistical Methods

Data were analyzed using the statistical package for social science (SPSS). The t-test was used to compare between two groups and ANOVA test was used for comparison between more than two groups. The following methods were obeyed: frequencies distribution, percentage distribution, range, mean & standard deviation and correlation co-efficient (r). P-values less than 0.05 were considered statistically significant. The Receiver Operating Characteristic curves (ROC curve analysis) were applied to assess the effect of therapy on IgE and PEFR.

Results

The demographic data of the studied groups were summarized in Table 1. All studied groups were matched regarding age, weight, height, and body mass index.

Table 1: Demographic data of groups A, B and control.

Item	Group A (LTA)	*P-value	Controls	**P-value	Group B (ICS)
Age(year)	8 ± 2	0.156	9 ± 2	0.144	10 ± 2
Weight (Kg)	31 ± 15	0.561	33 ± 9	0.903	32 ± 10
Height (cm)	127 ± 16	0.243	132 ± 10	0.438	136 ± 14
BMI (Kg/m^2)	17 ± 4	0.310	18 ± 3	0.071	16 ± 1
Asthma duration (years)	7 ± 2.7				8.3 ± 3

*P-value between Group A and controls; **P-value between Group B and controls

There was statistically significant difference between cases and controls as regards the absolute eosinophilic count, IgE, serum IL-5 and pulmonary function test parameters at the beginning of the study each of Ig E, eosinophilic count and IL-5 were statistically higher in cases compared to control. Meanwhile, pulmonary functions were lower (Table 2).

Table 2: Comparison between IgE, IL-5, eosinophils and pulmonary function tests during acute exacerbation of patients (A&B) and controls.

Item	Total cases (A+B) (Mean ± SD)	Controls (Mean ± SD)	p-value
IgE (IU/ml)	193 ± 170	43 ± 17	0.0001
IL-5 (pg/ml)	13 ± 16	5.5 ± 2.7	0.03
Eso (Cell/µL)	612 ± 492	195 ± 100	0.03
FVC (%)	64 ± 5	94 ± 5	0.0001
FEV1 (%)	69 ± 6	101 ± 11	0.0001
FEF25-75 (%)	80 ± 22	121 ± 23	0.0001
PEFR (%)	60 ± 14	104 ± 28	0.0001

Also, there was significant improvement of Ig E, IL-5, eosinophil and pulmonary functions after treatment in both groups (A and B). The efficacy of both drugs was comparable (Table 3).

Table 3: IL-5, IgE, eosinophils and PFTs during acute exacerbation and after treatment in groups A and B.

Item	Group A (LTA)		*P-value*	Group B (ICS)		*P-value*
	Acute exacerbation (Mean ± SD)	After treatment (Mean ± SD)		Acute exacerbation (Mean ± SD)	After treatment (Mean ± SD)	
IgE (IU/ml)	265.7 ±185	164.6±30.3	0.0001	119.4 ±118	74.6 ± 52.8	0.0200
IL-5 (pg/ml)	12.5± 15.5	5.7± 4.9	0.0200	14± 17.0	6.5± 4.4	0.0400
Eo (Cell/µL)	688.6±455.8	522±258.8	0.1000	534.5±257.5	324.1±177.2	0.0001
FVC %	63.6 ± 6.0	78.6 ± 6.4	0.0001	64.7 ± 5.0	78.2 ± 6.6	0.0001
FEV %	67.7 ± 5.9	85.7 ± 8.0	0.0001	71.0 ± 6.3	85.9 ± 7.6	0.0001
FEF 25-75%	76.5 ± 23.7	100.2±22.5	0.0020	82.7 ± 21.3	107 .5 ±23.7	0.0010
PEF %	56.8 ± 13.3	74.4 ± 10.0	0.0001	62.4 ± 13.5	80.2 ± 10.8	0.0001

Eso, eosinophils.

However, there was no correlation between IL-5 and each of eosinophilic count, IgE and pulmonary function tests (Table 4).

Table 4: Correlation between IL-5 and IgE, Eoinophils, and PFTs during acute exacerbation and after treatment in groups A and B.

Items	Time of testing	Group (A) & IL-5 (pg/ml)		Group (B) & IL-5 (pg/ml)	
		r	*p*	*r*	*p*
IgE (IU/ml)	Acute exacerbation	-0.045	0.858	0.239	0.311
	After treatment	-0.175	0.488	0.415	0.069
Eso (Cell/µL)	Acute exacerbation	0.409	0.092	0.154	0.517
	After treatment	-0.202	0.423	0.110	0.644
FVC (%)	Acute exacerbation	0.300	0.226	-0.240	0.308
	After treatment			-0.311	0.182
FEV1 (%)	Acute exacerbation	0.302	0.224	-0.401	0.080
	After treatment			-0.169	0.476
FEF25-75 (%)	Acute exacerbation	0.095	0.707	-0.152	0.523
	After treatment	0.074	0.772	0.170	0.474
PEFR (%)	Acute exacerbation	-0.224	0.371	0.017	0.942
	After treatment	0.100	0.692	0.259	0.270

Table 5 presents the Receiver Operating Characteristic curves (ROC curve analysis), showing significant difference of IgE and PEFR after treatment with leukotriene modifier.

Table 5: The effect of LT therapy on IgE and PEFR by ROC analysis.

Item	IgE	PEFR
Area under the curve	0.85	0.86
Confidence interval	0.542 – 0.873	0.122 – 0.461
Statistical significance (p-value)	0.025	0.024

Discussion

The development of asthma seems to involve numerous factors that include genetic, environmental and immunological factors [6]. Cytokines play a key role in orchestrating the chronic inflammation of asthma by recruiting, activating, and promoting the survival of multiple inflammatory cells in the respiratory tract [7]. Cytokines also direct and modify the inflammatory response in asthma and likely determine its severity [8]. Eosinophil is considered a key effector cell in the pathogenesis of allergic inflammation [9]. Increase in eosinophils often correlates with greater asthma severity. In our study, the absolute eosinophilic count in asthmatic children was significantly increased during acute exacerbation compared to control group. This was consistent with other studies [10]. This can be explained on the basis that, in case with atopic asthma, Cysteinyl-leukotrienes (Cys- Lts) which are potent bronchoconstrictors derived mainly from mast cells promote eosinophilia [11]. However, after 2 months of treatment with either leukotriene modifiers (LTA) or inhaled glucocorticosteroids (ICs) reduction in the blood eosinophil counts was observed. This result is in agreement with other workers [12] who reported that Leukotriene receptor antagonists, inhibits Cys-LTs, cytokines (e.g. IL-4 and IL-5) as well as eosinophil activation, leading to reduced eosinophilic migration into local tissue.

IgE plays a central role in the initiation and propagation of the inflammatory cascade and thus the allergic response [13]. In our study mean serum IgE level was significantly elevated in asthmatic children during acute exacerbation. This result is in accordance with Begum et al [14]. In atopic individuals, the IgE receptors result in secretion of abnormally high levels of IL4 from mast cells with overproduction of IgE antibodies [13]. However, significant reduction of IgE was observed after 2 months of treatment with either LTA or ICs. Similarly, Stelmach et al [11] reported significant decrease in levels of IgE in asthmatic children received either LTA or ICS for 6 months. Both corticosteroids and LTA appear to decrease production of IgE from B lymphocytes stimulated with IL-4[15]. Allergic diseases, including asthma, are characterized by inflammation with pronounced infiltration of eosinophils and CD4+ T cells. IL-5 is a cytokine that is highly specific for eosinophilic inflammation and was originally found as ‘T-cell replacing factor’ that is secreted from T cells to stimulate antibody production from activated B cells [16]. IL-5 seems to be the primary cytokine involved in vivo in the production, differentiation, maturation and activation of eosinophils [9].

In the present study serum IL-5 level was significantly elevated in asthmatic children compared to control group. This finding was also reported in other studies [17-19].

Interleukin-5 has been shown to increase the percentage of eosinophils in sputum and augment airway hyper responsiveness in asthma and antibodies that block IL-5 actions are effective in reducing eosinophilic inflammation and airway hyper responsiveness in various species [20]. In contrast to our results, Pukelsheim et al [21] reported no differences between healthy and asthmatic individuals in the serum IL-5.

In our study IL-5 level was significantly decreased to reach near control level after LTA or ICS treatment for 2 months. Similar to our results, Xie and his group [22] reported significant decrease in serum IL-5 in asthmatic children after montelukast treatment. Riliang et al [23] found that montelukast decreases the levels of IL-5 secreted by peripheral blood mononuclear cells in patients with asthma. On the other hand, non-significant decrease was observed in serum IL-5 after 2 months of treatment with inhaled corticosteroids. This is in agreement with other reports [10, 24] .They reported non- significant reduction of IL-5 after treatment with inhaled corticosteroids. However, this reported decrease of IL-5 may be related to the inhibitory role of inhaled corticosteroids as an anti- inflammatory drug on Th2 cells with subsequent suppression of IL-4 and IL-5 production [25].

The elevation of serum IL-5 and eosinophil count was associated with asthma manifestations and pulmonary function data. Anti inflammatory therapy led to decline in both parameters with subsequent improvement in both clinical and pulmonary functions data. This proves the direct role of IL-5 in asthma inflammatory process. The difference in response to either anti inflammatory drugs compared to other studies might be related to different genetic backgrounds of the studied groups.

Pulmonary function tests provide valuable information about severity of airway obstruction. Measurement of lung parameters (FVC%, FEV$_1$%, PER% and FEF 25% -75%) by spirometry to assess airflow limitation have gained widespread acceptance for the use in patients over 5 years of age. In our study, all lung parameters were significantly decreased in asthmatic children compared to controls. There was statistical significant improvement of all lung parameters after monteleukst or inhaled steroid treatment. In our results, Montelukast when compared to inhaled corticosteroid demonstrated similar improvements in pulmonary function tests improvement.

This finding agrees with other reports [26, 27] who found relative efficacies in the two treatment groups. In contrast to our results Garcia et al [28] concluded that montelukast was more effective than fluticasone in increasing the percentage of asthma rescue free days. On the other hand, Meltzer et al [29] found that treatment with fluticasone significantly improved pulmonary function, asthma symptom scores and the percentage of symptom free days when compared to montelukast.

In conclusion, serum IL-5 level seems to have an important role in pathogenesis of asthma. Relative efficacies of the two treatment groups (ICs & LTA) are similar in partly controlled asthmatic children. Both treatments led to decline in IL-5, IgE levels and eosinophil count.

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