IgE Production in Allergic Asthmatic Patients with Different Asthma Control Status

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***Background**: Although much is known about the fact that IgE-mediated allergic inflammatory response contributes to airway inflammation, bronchial hyperresponsiveness, and asthma severity, little is known about the degree of IgE response in allergic asthmatics during treatment.*
***Objective**: To determine the amount of total serum IgE among allergic asthmatic patients with various asthma controls.*
***Material and Method**: A total of 190 non-smoking patients with allergic asthma were divided into three groups by using the asthma control definition according to the GINA 2006 criteria. There were 64 well-controlled, 88 partly-controlled, and 38 uncontrolled. After study entry, patients underwent lung function test, methacholine challenge and skin prick test to establish allergic status. Peripheral venous blood specimens were collected to measure total IgE and absolute eosinophil numbers. The data are expressed as mean $\pm$ SD.*
***Results**: The logarithm of total serum IgE was significantly higher in subjects with uncontrolled allergic asthma than in those with well-controlled disease ($p < .0001$). IgE response in uncontrolled asthmatics was still high despite having been treated with ICS at a dose which was significantly high when compared with well-controlled subjects (1075.4 $\pm$ 420 vs. 703.5 $\pm$ 355, $p < .0001$). The logarithm of total serum IgE was associated with increased blood eosinophil counts ($r = 0.25$, p .0007) among three asthmatic groups and with decreased prebronchodilator FEV_1 ($r = -0.42$, $p = .0075$) and PC_{20} ($r = -0.36$, $p = .04$) only in uncontrolled group.*
***Conclusion**: In allergic asthmatic patients with various disease control stages, there are differences in IgE immune response. Both high and non-suppressible total serum IgE response may be involved in the development of uncontrolled asthma.*

***Keywords:** Allergic asthma; Asthma control; Immunoglobulin E*

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Allergic asthma is a chronic inflammatory airway disease which is driven by Th2-derived cytokines such as interleukin (IL)-4, IL-5 and IL-13[1]. IL-5 is required for eosinophil activation and survival[2-4]. IL-4 induces the differentiation of naive T-cells into Th2 cells[5,6] and B-cell isotype switching to IgE[5], enhances high-affinity and low-affinity IgE receptor expression and promotes the accumulation of eosinophils in the airways, all of which cause allergic inflammation in response to an aeroallergen. The allergic inflammatory cascade is initiated with the interaction of the allergen with IgE that occurs on the surface of mast cells which mediates intracellular signaling through the high affinity IgE receptors (FceR1) and results in mast cell activation and degranulation[7]. An array of mediators released from mast cells can, in turn, regulate eosinophil activation[8].

The Global Initiative for Asthma (GINA) guide-

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line recommends evaluating asthma control status after treatment at intervals in order to step up or step down asthma medications[9]. The evaluation of the therapeutic response to asthma treatment is based on the levels of asthma control which are well-controlled, partly-controlled and uncontrolled stages, according to the criteria of GINA using the frequency of nocturnal and daytime symptoms, the need of reliever medication, lung function test and the number of exacerbations. The presence of asthma exacerbation is one of the most important parameter in differentiating between well-controlled and uncontrolled asthma. After the maintenance treatment patients with well-controlled asthma do not develop an exacerbation whereas patients with uncontrolled asthma may exacerbate at any time. In patients with moderate or severe persistent asthma, control may not be achieved with an inhaled corticosteroid or even a combination inhaler containing a corticosteroid and a long-acting β_2 agonist which is often more effective than the former in preventing asthma exacerbation. Maintenance recombinant anti-IgE monoclonal antibodies may be given because the strategy has been shown to be effective for severe asthma in reducing the number of exacerbations as demonstrated in several studies[10-13]. Although the studies suggested the involvement of aeroallergen-triggered IgE response in asthma exacerbation and worsening of airway inflammation, little is known about IgE production in patients with various asthma controls.

Therefore, we investigated IgE responses in patients with allergic asthma who achieved well-controlled or partly-controlled status and who were uncontrolled with an inhaled corticosteroid or a combination inhaler containing a corticosteroid and a long-acting β_2 agonist or other additional asthma medications, with the exception of systemic corticosteroids and recombinant anti-IgE monoclonal antibodies. We found that patients with uncontrolled allergic asthma showed higher IgE production than those with well-controlled and partly-controlled asthma and this response negatively correlated with FEV_1 and PC_{20} and the levels of IgE among all asthmatic patients positively correlated with peripheral blood eosinophilia.

Material and Method

Subject participants

Non-smoking allergic asthmatic subjects were recruited from asthma clinics at Siriraj Hospital. Eligible subjects were between the ages of 15 and 80 years, had physician-diagnosed asthma according to the American Thoracic Society criteria. Subjects demonstrated a reversibility of FEV_1 after therapy with nebulized albuterol (2.5 mg) of $\geq$ 12% and a provocative concentration of a methacholine causing a 20% fall in FEV_1 (PC_{20}) of $\leq$ 4 mg/mL and their asthma medications were not adjusted within 3 months prior to study entry. Allergic status was defined by the presence of a positive skin prick test to at least one of four common aeroallergens (grass pollen, cat dander, *Dermatophagoides pteronyssinus, Aspergillus fumigatus*). None had received therapy with oral corticosteroids in the 3 months and with recombinant anti-IgE monoclonal antibodies prior to the study nor had they had any asthma exacerbation or respiratory tract infection within 4 weeks before the study or co-morbid medical illnesses. Subjects with history or clinical signs of parasitic infection, chronic inflammatory diseases, and HIV-infection were excluded. Written informed consent was obtained from each patient, and the study was approved by the Ethics Committee of Siriraj Hospital.

All subjects underwent thorough clinical evaluation (age, sex, occupation, smoking status, physical examination) and their current asthma medications were reviewed, skin prick test with allergen extracts and lung function test (spirometry) were performed, as well as nonspecific bronchial provocation (methacholine) to verify bronchial hyperresponsiveness (but not if baseline FEV_1 was less than 50% predicted or 1.0 L)[14]. A blood sample was drawn to determine serum total IgE levels.

The level of asthma control was determined by the GINA 2006 criteria that used information gathered from a questionnaire and spirometric data[9]. The assessment of asthma control was made while all subjects were on the regular use of appropriate asthma medications. All subjects were classified as having well-controlled or partly controlled or uncontrolled asthma on the basis of 6 criteria:

1. Use of reliever/rescue treatment
2. Presence of daytime asthma symptoms
3. Presence of nocturnal asthma symptoms
4. FEV_1 < 80% of race-corrected predicted (measured at the study visit)
5. Limitation of daily activities
6. Presence of $\geq$ 1 exacerbation of the previous year

Subjects were classified as well controlled if they did not meet any of the above criteria, were classified as partly controlled if they met any of the above criteria in any week, and were classified as uncontrolled if they met $\geq$ 3 of the above criteria.

Lung function measurements and methacholine challenge

FEV_1 and FVC were measured using a dry wedge spirometer (Vitalograph, Buckingham, UK). Values are expressed as the percent of predicted normal values. Baseline values were measured after 15 min of rest and were taken as the highest of three readings. Single readings only were taken at other times. The methacholine PC20 was determined by the linear interpolation of the concentration-FEV_1 response curve as previously described[14].

Skin prick test (SPT)

Skin prick test carried out by aeroallergen skin prick testing of the right forearm of each subjects using extracts of *Dermatophagoides pteronyssinus*, *Amaranthus hybridus*, *Periplaneta americana*, *Cynodon dactylon*, cat epithelium (*Felis catus*), dog epithelium (*Canis familiaris*), *Ceiba pentandra*, mold mix *(Alternaria alternata, Aspergillus niger, Bipolaris sorokiniana, penicillium notatum* and *Cladosporium sphaerospermum)*, and Aspergillus mix *(Amstelodami, A. flavus, A. fumigatus, A. nidulans, A. niger)*. Saline and histamine were used as negative and positive controls, respectively. Wheal size was read after 15 minutes and the SPT response was considered positive with a wheal diameter to the particular allergen of 3 mm or larger than that produced by NaCl.

IgE measurement

Total serum IgE was measured in duplicate for all subjects with asthma by using latex agglutination test (N latex IgE mono, Dade Behring, Germany) with automatic system (BN prospec version 1.12, Dade Behring Inc, Germany). Total IgE levels were expressed as IU/ml. The range of detection limit was between 4.76 IU/ml and 40,000 IU/ml.

Statistical analysis

Data are presented as mean $\pm$ SD. Total IgE (adjusted for age and sex), blood eosinophils, and PC_{20} methacholine data were log-transformed to achieve a normal distribution. The differences in clinical characteristics of three asthma control groups (well-controlled, partly-controlled, and uncontrolled asthma) were examined by Pearson Chi-square test. For continuous variables, an ANOVA was performed to examine significant differences between asthma control groups. Tukey method was performed for individual comparisons when an overall F-test indicated significant differences among mean values. Kruskal-Wallis test was performed for ordinal data. The relationship between the serum total IgE and FEV_1, PC_{20}, and peripheral blood eosinophil numbers was achieved using Spearman's rank correlation test. Two tailed tests were performed and a p-value of less than 0.05 was considered significant. The SPSS V. 10.5 statistical analysis software was used for this analysis (SPSS Ino., Chicago, IL).

Results

Subject characteristics

One hundred and ninety allergic asthmatic patients who were on the regular use of anti-inflammatory therapy for three months without adjusting treatment before the evaluation of achievement in asthma control were recruited into the study. Table 1 summarises their clinical characteristics. According to the GINA criteria, 64 patients were well-controlled asthmatics, 88 partly-controlled, and 38 uncontrolled. The age of patients with uncontrolled asthma was higher than well-

Table 1. Subject demographics and medication use

	Group 1: Well controlled (n = 64)	Group 2: Partly controlled (n = 88)	Group 3: Uncontrolled (n = 38)	p-value
Demographics				
Current age (y)	50.2 $\pm$ 15.1	50.3 $\pm$ 14.1	57.2 $\pm$ 11.2	$0.024^{(2,3)}$
Age of asthma onset(y)	28.5 $\pm$ 19.5	29.6 $\pm$ 16.6	27.8 $\pm$ 17.7	0.86
Asthma duration	21.7 $\pm$ 17.3	20.7 $\pm$ 14.7	29.4 $\pm$ 15.4	$0.016^{(2,3)}$
Number of asthma medications	1.26 $\pm$ 0.6	1.71 $\pm$ 0.8	1.92 $\pm$ 0.9	$<0.0001^{(1,2)}$

Means $\pm$ SD are shown. pvalues for comparison among groups were derived from ANOVA and Chi-Square test as appropriate. 1 = comparison between group 1 and 2; 2 = comparison between group 1 and 3; 3 = comparison between group 2 and 3.

controlled and partly controlled asthmatics. Duration of being asthma in uncontrolled asthmatics was longer than the other two groups. In addition, the number of asthma medications which patients in uncontrolled and partly controlled groups administered more than the well-controlled group.

IgE levels and other study parameters among the various GINA asthma control groups

Serum total IgE concentrations were significantly higher in patients with uncontrolled asthma than in those with well-controlled and partly-controlled disease ($p < .0001$) (Table 1). We found that the onset of asthma did not affect the levels of IgE production.

In comparison with patients with well-controlled asthma, FEV_1, FVC, FEF_{25-75}, and PC_{20} values of patients with uncontrolled asthma showed statistically lower significance, whereas peripheral blood eosinophil counts were significantly higher in those with uncontrolled disease compared to those with well controlled disease ($p = .004$) (Table 2). However, the numbers of prick test positivity to common seven allergens were not different among the various GINA asthma control groups.

Relationships between total serum IgE and lung function indices, PC_{20} and peripheral blood eosinophil counts

Mean basal prebronchodilator FEV_1 and PC_{20} but not FEV_1/FVC ratios and FEV_1% were inversely associated with logarithm serum IgE values in uncontrolled asthma group ($r = -0.42$, $p = .0075$, $r = -0.36$, $p = .04$, respectively; Fig. 1), whereas peripheral blood eosinophil counts were positively associated with serum total IgE levels ($r = 0.25$, p .0007; Fig. 1). However, none of these associations between log IgE and lung function indices was demonstrated in other asthma control groups.

Discussion

The present study demonstrates that the levels of serum total IgE in subjects with uncontrolled allergic asthma are significantly higher than those in well-controlled asthmatics. In addition, the results of our study suggest that the regular use of appropriate anti-inflammatory treatment, in particular inhaled corticosteroids, did not have much effect on serum total IgE levels.

Several studies suggested that total serum IgE correlated with asthma severity as evaluated before anti-inflammatory therapy[15,16]. However, little is known about IgE responses in allergic asthmatic subjects during a period on therapy. Our data suggested that patients with uncontrolled allergic asthma had significantly high serum IgE levels compared to those with

Table 2. Lung function indices and other study parameters

	Group 1: well controlled		Group 2: partly controlled		Group 3: uncontrolled		
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	*P*-value
Baseline lung function							
FEV_1%	64	86.8 ±10.3	88	65.1 ± 18.6	38	63.1 ± 20.8	<0.0001[1,2]
Pre-bronchodilator FEV_1 (L)	64	1.99 ± 0.64	88	1.49 ± 0.58	38	1.35 ± 0.55	<0.0001[1,2]
FVC (L)	64	2.61 ± 0.75	88	2.22 ± 0.7	38	1.94 ± 0.77	<0.0001[1,2]
FEV_1%FVC	64	76.5 ± 12.7	88	67.5 ± 18.8	38	73.7 ± 30.4	0.02[1]
FEF_{25-75}%	64	1.58 ± 0.59	88	1.1 ± 0.6	38	0.96 ± 0.48	<0.0001[1,2]
Methacholine PC_{20} (log, mg/mL)	60	0.42 ± 0.72	60	-0.31 ± 0.83	32	-0.31 ± 0.93	<0.0001[1,2]
Blood eosinophils (log)	62	1.98 ± 0.47	84	2.13 ± 0.64	32	2.38 ± 0.45	0.004[2]
Total serum IgE (log)	64	1.89 ± 0.57	88	2.45 ± 0.57	38	2.72 ± 0.34	<0.0001[1-3]
Number of positive skin test*	61	4 [1, 9]	88	5 [1, 9]	35	5 [1, 9]	0.942
Dose of ICS (mg/d)	63	703.5 ± 355	88	904.3 ± 448	37	1075.4 ± 420	<0.0001[1,2]

Means ± SD are shown. P-values for comparison among groups were derived from ANOVA.
* represents Median [Min, Max], 1 = comparison between group 1 and 2; 2 = comparison between group 1 and 3; 3 = comparison between group 2 and 3.
Abbreviations: FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; PC_{20}, provocative concentration causing a 20% fall in FEV_1

well-controlled asthma and those with partly-controlled asthma. The high IgE response could not be attenuated although the uncontrolled allergic asthmatics were on a regular use regimen of inhaled corticosteroids at higher dose compared with the others. In addition, subjects with uncontrolled disease were treated with a significantly greater number of asthma medications compared with the well-controlled group. These data also suggested that the uncontrolled condition might be as a consequence of high IgE production.

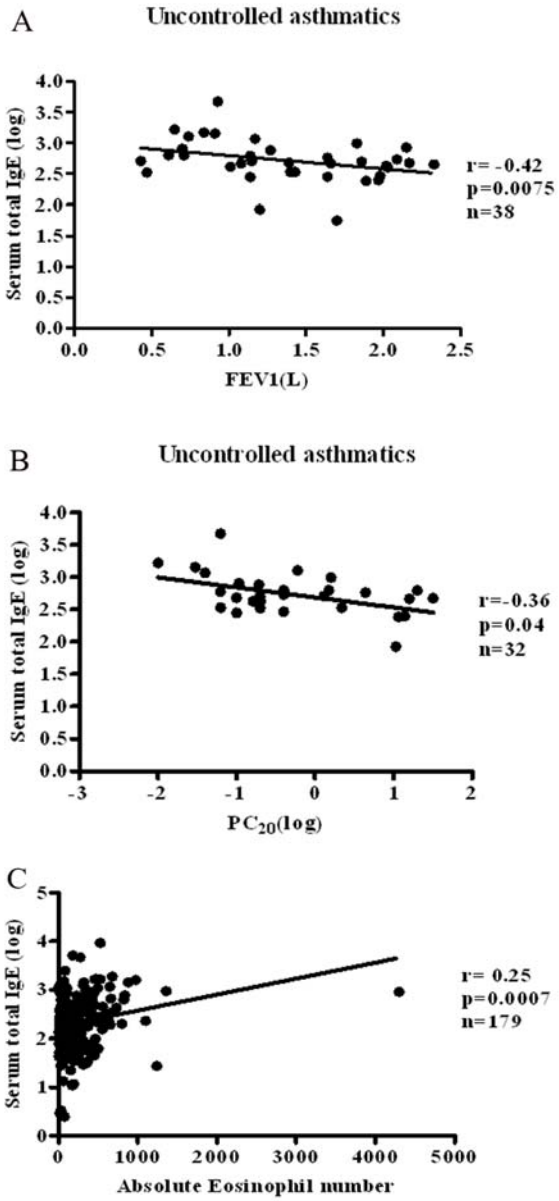

Fig 1. Relationship between log IgE and pre-bronchodilator FEV_1 (A), log PC_{20} (B) in subjects with uncontrolled asthma and peripheral blood eosinophil counts (C) in all asthmatic patients. Symbols represent asthmatic individuals. IgE production correlated negatively and significantly with FEV_1 and PC_{20}, whereas it correlated positively and significantly with peripheral blood eosinophilia

As previous studies have failed to demonstrate associations between asthma symptoms and markers of atopic sensitization, investigators have concluded that atopy may have a lesser role in determining asthma control than in determining severity[17]. This speculation is not supported by our own and recent other studies[18] demonstrating that patients with uncontrolled allergic asthma had high IgE response which was significantly associated with FEV_1 and PC_{20}. The GINA guideline on asthma clearly defines the goals of asthma therapy and identify persistent symptoms and lung function abnormalities as evidence of poor asthma control[9]. Apart from the above recommendations, the present study may suggest that IgE response should be evaluated among allergic asthmatic patients with uncontrolled stage and also that future studies are required to determine whether calibrating the corticosteroid dose according to the level of total IgE is a feasible approach in asthma management.

Many studies have shown the correlation of BHR and serum total IgE levels[19-22]. Present data indicate that the presence of a high IgE concentration only in subjects with uncontrolled allergic asthma relates to BHR measured simultaneously. In addition, our study indicates that IgE production was significantly albeit not strongly associated with peripheral blood eosinophilia, implying that development of BHR and eosinophilic inflammatory responses requires IgE production, which is inconsistent with murine models demonstrating equivalent degrees of eosinophilic inflammation and BHR elicited by means of allergen inhalation in wild-type and IgE deficient mice[23,24]. In contrast to uncontrolled allergic asthmatics, we observed no significant relationship between BHR and IgE concentrations in the well-controlled group. The different relationship of these factors among these asthma control groups may imply the important role of IgE in the development of uncontrolled asthma status.

It is well known that corticosteroids are effective in increasing lung function, reducing bronchial hyperresponsiveness, preventing exacerbations and hospitalization[25,26] and in reducing airway inflammation[27,28]. Topical corticosteroids have beneficial effect on local IgE production only in patients with allergic

rhinitis[29,30] but not in those with asthma, despite being on systemic corticosteroids[31]. The mean baseline FEV_1 and PC_{20} was relatively low in the uncontrolled group in spite of having been treated with ICS for 3 months prior to evaluation of lung function test, possibly indicating that our allergic asthmatics with poor disease control experienced unimproved pulmonary function connected with IgE binding on the surface of effector cells, which causes the release of pro-inflammatory mediators. Although we did not measure local IgE production which has been recently reported to be present in the small airways[31], the possibility that ICS could inhibit local IgE levels could be excluded because, if this is the case, we should demonstrate the improvement of FEF_{25-75} values in allergic asthmatics with uncontrolled disease who were persistently on a high dose of ICS when compared with those with well-controlled asthma.

Our study has a number of limitations. Because of high prevalence of parasitic infection, we could not totally exclude the possibility that the increase of IgE production may be immune response to parasitic infections to some extent although stool examination was tested in some patients who had extremely high IgE levels. In addition, we did not do serial IgE measurement so it remains unknown whether elevated IgE levels in patients with partly controlled or uncontrolled asthma were persistent or transient.

In conclusion, the present study suggests that high and non-suppressible IgE production may lead to the development of uncontrolled asthma.

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การสร้าง IgE ในผู้ป่วยโรคหืดที่มีระดับการควบคุมอาการแตกต่างกัน

กิตติพงศ์ มณีโชติสุวรรณ, พิมฑิราห์ สุจริตวงศานนท์, ทัศนียา สุธรรมสมัย

ภูมิหลัง: *เป็นที่ทราบดีว่า IgE เกี่ยวข้องในการทำให้เกิดหลอดลมอักเสบ หลอดลมไวต่อสิ่งกระตุ้น และมีส่วนสัมพันธ์กับความรุนแรงของโรคหืด อย่างไรก็ตามระดับการตอบสนองของ IgE ในผู้ป่วย allergic asthma ระหว่างที่กำลังรักษายังไม่เป็นที่ทราบกัน*

วัตถุประสงค์: *เพื่อวัดปริมาณของ total IgE ในซีรัมของผู้ป่วย allergic asthma ที่มีระดับการ ควบคุมโรคแตกต่างกัน*

วัสดุและวิธีการ: *ผู้วิจัยรวบรวมและจำแนกผู้ป่วย allergic asthma จำนวนทั้งหมด 190 คนตามระดับการควบคุมโรคอาศัยคำนิยามของ GINA ปี พศ 2549 ออกเป็น 3 กลุ่ม คือผู้ป่วยกลุ่มควบคุมอาการได้ 64 ราย กลุ่มควบคุมอาการไม่ได้ดี 88 ราย และกลุ่มควบคุมอาการไม่ได้ 38 ราย โดยผู้ป่วยต้องไม่มีประวัติปรับเปลี่ยนรักษาโรคหืดเป็นเวลานานติดต่อกัน 3 เดือนก่อนเข้าการศึกษา ผู้ป่วยที่เข้าร่วมการศึกษาได้รับการตรวจสมรรถภาพการทำงานของปอด กระตุ้นหลอดลมด้วยสาร methacholine การทดสอบการแพ้สารก่อภูมิแพ้ทางผิวหนัง เพื่อให้แน่ชัดว่าเป็น allergic asthma รวมทั้งการตรวจหาระดับ total IgE ในเลือด*

ผลการศึกษา: *ระดับของ total IgE ของผู้ป่วย allergic asthma ที่ควบคุมอาการไม่ได้ สูงกว่าผู้ป่วย allergic asthma ที่ควบคุมอาการได้ อย่างมีนัยสำคัญทางสถิติ (*P < *.0001) แม้ว่าจะรักษาด้วยยา corticosteroid ชนิดสูดพ่นขนาดสูงกว่ากลุ่มที่ควบคุมอาการได้ (1075.4 ± 420* vs *703.5 ± 355,* P<*.0001) นอกจากนั้นระดับของ total IgE มีความสัมพันธ์โดยตรงกับจำนวน eosinophil ในเลือด (r = 0.25,* P *.0007) ของทั้งสามกลุ่มและมีความสัมพันธ์แบบผกผันกับค่า pre-bronchodilator FEV_1 (r = -0.42,* P = *.0075) และ PC_{20} (r = -0.36,* P = *.04) ซึ่งพบเฉพาะกลุ่มผู้ป่วยโรคหืดที่ควบคุมอาการไม่ได้*

สรุป: *ผู้ป่วย allergic asthma ที่มีระดับการควบคุมอาการได้ต่างกันจะมี IgE immune response แตกต่างกัน และการตอบสนองของ IgE ไม่ลดลงหลังรักษาด้วยยา corticosteroid ชนิดสูดพ่น จึงอาจมีส่วนทำให้ผู้ป่วยโรคหืดควบคุมอาการไม่ได้*