



IL-4 and IL-6 in Bronchial Asthma Does IL-6 Plays More Important Role than IL-4? A Preliminary Study

Authors

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Abstract

Summary: Cytokines IL-4, 5, 6 and 13 plays an important role in the pathogenesis & chronicity of bronchial Asthma. Main purpose of the study was to see role of IL-4 & IL-6 in allergic disease.

Material & Method: Total 58 cases of bronchial asthma in which 10 cases were having allergic rhinitis and 07 had urticaria, along with 20 healthy controls were taken for study between period of November 13 to December 14.

Result: Among 58 patients of asthma, 10 had associated rhinitis and 07 cases had urticaria. Out of 58 cases 58.62% patients were male and 41.38% patients were females. Total 13 patients were children of age group 3-15 year in which males were 23.53% & females were 20.83% . Most common age group was 16-30 years in which 54.16 % were female and 47.05% were male. Total 42 cases (72.41%) were between 3 to 30 years. IL-4 was raised significantly in asthma cases in 25% cases. Similarly, IL-6 was significantly elevated in 48.27% patients of asthma. Thus our study concludes that IL-6 plays more role in pathogenesis of asthma than IL-4. Monoclonal antibody to IL-6 may be tried on this cases.

Keyword: Bronchial Asthma, Allergic rhinitis, urticaria, IL-4, IL-6, Cytokines.

Introduction

Allergic diseases are mediated by IgE antibody which after fixing on membrane of mast cells interact with allergens and produces degranulation of mast cells and releases preformed mediators from mast cells like histamine, proteases, neutrophil and monocyte chemotactic factor, heparin, chondroitin sulphate, acid hydrolases which bring immediate reaction & leads to vasodilatation, increased nasal discharge, sneezing, broncho constriction and urticaria^(1,2,3)

Mast cell also synthesizes leukotriens (B4, C4 & D4) and prostaglandins, platelet activating factor from membrane phospholipids. It also synthesizes cytokines, TNF α and IL-1, which recruits TH2

and other inflammatory cell and bring the late phase response which sustains allergy for several weeks to month.^(1,3,4,5)

Cytokines plays a very important role in the pathogenesis of bronchial asthma and in orchestrating inflammatory response⁽⁶⁾. It is said that most of the allergic diseases are due to imbalance between Th1 & Th2 CD4 helper cells. In bronchial asthma Th1 cytokines (IL-2, IFN γ) are reduced while Th2 cytokines IL-4, IL-5, IL-6, IL-13, IL-10 are increased.^(7,8,9)

This disbalance is due to less exposure to infection and intestinal parasites in developed countries due to good hygiene⁽³⁾.

Allergic bronchial asthma is a chronic inflammatory disease of the air ways that occurs in response to inhaled allergen eg. ragweed, cat, danders, house dust mite & fungi ⁽⁹⁾.

IL-4 increases IgE production ⁽¹⁰⁾ by causing isotype switching in B cells, increases Vascular Cell Adhesion Molecules (VCAM) on endothelial cells which produces adhesion of T cell, eosinophils, basophils & monocytes ⁽¹¹⁾. In some study it is also claimed that IL-4 produces bronchial hyper responsiveness & inflammation of lung ⁽¹²⁾. It causes Th2 differentiation. IL-4 stimulates mast cell growth and regulate IgE synthesis ⁽¹³⁾ and antagonizes TH1 cytokine activity ⁽⁶⁾. IL-5 cause eosinophil survival ⁽³⁾, differentiation and migration while IL-13 induces mucus metaplasia and airway hyper responsiveness ^(14,15,16). IL-4, 5, 13 causes late and ongoing allergic symptoms ⁽⁵⁾.

Recently role of Th17 cells and its cytokines IL-17 A and E has also become important. Immune response to Th2/Th17 differentiation depends upon allergens & lung involvement. IL-33 secreted by lung epithelial cells, promotes Th2 differentiation and IL-5 productions ⁽¹⁷⁾.

IL-17 is a pro inflammatory cytokines which causes production of Granulocyte Monocyte Colony Stimulatory Factor (GM-CSF), IL-6 and intercellular adhesion molecule (ICAM), and proliferation of T Cells ⁽¹⁸⁾.

IL-6 is a glycoprotein of 21Kd produced by cells of innate immunity such as macrophages, dendritic cell, mast cells and neutrophil. In

additions it can also be secreted by CD4 cell endothelial cells, fibroblast, astrocytes, adipocyte and malignant cells ^(19,20) & epithelial cells ⁽²¹⁾

IL-6 is also produced by inflammatory cells and by lung epithelial cells, in response to allergens and other stimuli eg. respiratory viruses and exercise ^(22,23,24) in cases of asthma.

IL-6 is a general marker of inflammation ⁽²⁵⁾. It also produces T cell growth & differentiation ⁽²⁶⁾.

Aim of present study was to see role of IL-4 and IL-6 in patients of bronchial asthma.

Material & Method

Total 58 cases of bronchial asthma in which 10 cases were having allergic rhinitis and 07 had urticaria, along with 20 healthy controls were taken for study between period of November 13 to December 14.

Patients were examined by clinicians. All patients had elevated serum IgE and had classical feature of Asthma. Detail clinical history were recorded. Serum IL-6 and IL-4 were done by ELISA Kit of Diasource company.

It was supplied by M/s Immuno Shop, India Private Limited, 309, Raheja, Arcade, Sector II, CBD Belapur, Navi Mumbai-400614.

Result

In total 72.4% patients were between 3 to 30 years. Sex wise distribution revealed that males were more affected (58.6%) than females. Mean age of female patients were lower than male .

Table I : Age and sex wise distribution of patients

Age in years	Males		Females		Total	
	No.	%	No.	%	No.	%
3 to 15	08	23.53	05	20.83	13	22.41
16 to 30	16	47.05	13	54.16	29	50.00
31 to 40	05	14.70	04	16.66	09	15.51
41 to 50	02	5.88	0	0	02	3.44
>50 years	03	8.82	02	8.33	05	8.62
Total	34	58.62	24	41.38	58	-
Mean age of patient	29.94 ± 13.6 year	25.92 ± 13.74 year				

Serum IL-4 levels were within normal limit (L20 pg/ml) in 74.1% patients while in controls all cases had IL-4 levels below 20 pg/ml. In 25.9%

patients, serum IL-4 was raised which was significant as compared to control.

Table II : Serum IL-4 levels in allergic diseases and healthy control

Groups (Number of cases)	Serum IL-4 < 20 pg/ml		Serum IL-4 >20 Pg/ml		Chi square AVB	P value
	No.	%	No.	%		
(A) Allergic diseases (58)	43	74.1%	15	25.9%	6.103	.016
(B) Controls (20)	19	100	0	0.0		

All cases in which IL – 4 was raised either had allergic rhinitis or urticaria along with asthma. Serum IL-6 in patients in 51% cases was below 20pg/ml and in 48.27% patient its value was above 20 pg/ml. Rise of IL-6 in Asthma cases was highly significant. In normal controls level of IL-4

varied from 0.3 to 11.75 pg/ml & IL-6 level ranged from 0.42 to 41.42 pg/ml. In controls, only two had raised IL-6 of 22.47 pg/ml and another had 41.47 pg/ml. In patients IL-4 levels varied from 0.96 to 233.63 pg/ml while levels of IL-6 varied from 0.7 to 1212.72 pg/ml

Table III : Serum IL-6 levels in allergic diseases and healthy controls.

Groups (Number of cases)	IL-6 < 20 pg/ml		IL-6 >20 pg/ml		AVSB Chi Square	P Value
	No.	%	No.	%		
(A) Allergic diseases (58)	30	51.7%	28	48.27	8.576	0.003
(B) Controls (20)	17	89.47	2	10.52		

Discussion

In present study we found increase of IL-4 in only 25% cases of bronchial asthma & this increase was significant. Similar to our study some recent study⁽¹³⁾ also reported significant increase in IL-4 in asthma and other allergy. Some workers reported that IL-4 was associated with increased IgE production but not with bronchial hyper responsiveness⁽¹²⁾.

IL-6 is another very important cytokines for bronchial asthma. It regulates Th1 & Th2 balance, promote IL-4 production, inhibit Th1 differentiation^(26,27). IL-6 together with TGF- β 1 promote Th2 differentiation.

Increased level of IL-6 in serum have been demonstrated in bronchoalveolar lavage fluid of asthmatic patients^(24,29). IL-13 is also raised in bronchial asthma which correlates with increased IL-6 & impaired lung function⁽⁹⁾. Hence IL-6 can be potential new target for treatment of bronchial asthma⁽⁹⁾.

IL-6 also increases mucus secretion. In wild type of mice, blockade of IL-6 reduces development of allergic airway inflammation⁽³⁰⁾. There are reports that in bronchial asthma there is altered muscle function & chronic inflammation⁽³¹⁾.

In present study 48.27% patient of asthma had significantly elevated serum IL-6. Similar to our study several workers^(32,33,34) also found increased levels of interleukin 6 in bronchial asthma.. There is negative correlation between IL-6 and FEVI in asthmatic patient^(32,34).

Thus our study concludes that IL-6 plays more important role in pathogenesis of asthma than IL-4. Monoclonal antibody against IL-6 may be tried in these cases.

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