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Increased serum IL-17 is an independent risk factor for severe asthma

Ioana Agache [a,*], Cristina Ciobanu [b], Costel Agache [b], Mariana Anghel [c]

[a] *Transylvania University, Faculty of Medicine, Department of Allergy and Clinical Immunology; B-ul Eroilor 29, Brasov 500036, Romania*
[b] *Theramed Medical Center, Department of Allergy and Clinical Immunology; Spatarul Luca Arbore 16, Brasov 500112, Romania*
[c] *Brasov County Hospital, Immunology Lab; Calea Bucuresti 25-27, Brasov 500326, Romania*

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Summary
Background: IL-17 expression was found to be associated with many inflammatory diseases in humans, such as rheumatoid arthritis, asthma, systemic lupus erythematosus and allograft rejection and many in vitro studies have indicated a proinflammatory function for IL-17.
Objective: Prognostic value of increased serum IL-17 in asthma patients.
Methods: Serum IL-17 (ELISA) was measured in 85 asthma patients (pts), mean age 46.99 ± 14.1 years, 61% females, 23 mild persistent, 26 moderate persistent and 36 severe persistent asthma. Using multiple regression analysis (STATISTICA 7), increased serum IL-17 (>20 pg/ml) was tested as risk factor for severe asthma in comparison with ''traditional'' risk factors: smoke, NSAID intolerance, obesity, chronic rhinosinusitis, blood eosinophilia, FEV_1 at baseline < 50% predicted (low FEV_1).
Results: Medium serum IL-17 values were 14.21 pg/ml in mild asthma, 12.22 pg/ml in moderate asthma and 24.72 pg/ml in severe asthma. IL-17 values > 20 pg/ml were encountered in 3(13%) mild asthma pts ($p < 0.001$ vs. severe asthma), 2(8%) moderate asthma pts. ($p < 0.001$ vs. severe asthma), and in 11(31%) severe asthma pts. For severe asthma multiple regression analysis revealed as independent risk factors IL-17 ($p = 0.000290$), NSAID intolerance ($p = 0.000585$) and low FEV_1 ($p = 0.000059$).
Conclusions: IL-17 is increased in severe asthma compared to mild/moderate forms of the disease and values above 20 pg/ml are an independent risk factor for severe asthma.

* Corresponding author. Spatarul Luca Arbore 16, Brasov 500112, Romania. Tel.: +40 727 849321; fax: +40 268 471814.
E-mail address: ibrumaru@unitbv.ro (I. Agache).

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Introduction

IL-17A is a newly described proinflammatory cytokine secreted by a subtype of T helper lymphocytes, Th17.[1] Increased IL-17A expression was found to be associated with many chronic inflammatory diseases in humans, such as rheumatoid arthritis, asthma, systemic lupus erythematosus and allograft rejection.[2]

The role of IL-17/Th17 cells in asthma is yet unclear. In a murine model of asthma IL-23 and Th17 cells not only induce Th17-cell-mediated neutrophilic airway inflammation, but also up-regulate Th2-cell-mediated eosinophilic airway inflammation.[3]

In the sputum of asthma patients, including moderate/severe asthma under inhaled steroid treatment, the IL-17 mRNA was increased and correlated with increased IL-8 mRNA and with sputum neutrophilia. IL-17 mRNA was also correlated with mRNA for the CD3 gamma chain, thus suggesting the lymphocytic origin (Th17) of the cytokine.[4] IL-17A and IL-17F were suggested to promote neutrophilic inflammation of the airways through increased release of CXCL1 and CXCL8 (IL-8) from bronchial epithelium.[5] Tissue IL-17 expression is increased in bronchial biopsies from patients with asthma and stimulates bronchial fibroblasts to secrete cytokines.[6] In another study increased sputum IL-17 was correlated with methacholine bronchial hyperreactivity.[7] However, in an attempt to identify the specific sputum biomarkers that distinguish different subtypes of severe asthma, neither IL-17 or other cytokine measured in induced sputum correlated with persistent airway obstruction.[8]

Systemic inflammation associated with asthma and it's relation to asthma severity is well demonstrated and recognized.[9–11] There are few data on serum IL-17A levels in asthma patients. In one study allergic asthma patients had higher plasma IL-17 and IL-6 concentrations than normal controls, although the differences were not statistically significant, while IL-18, IL-12, IL-10, IL-13 were significantly higher compared to controls.[12]

The current study was undertaken to determine whether increased serum IL-17A has a prognostic value for adult asthma patients.

Methods

Study design and subjects

The study protocol was approved by the local Ethics Committee (IRB). The study has a cross-sectional design and is based both in a private setting and in a community hospital. Adults/adolescents patients with doctor diagnosed persistent asthma were selected both from the private practice and the hospital database. 233 subjects were contacted by phone, 180 attended the clinic and received both written and oral information, 127 subjects gave their oral consent to participate in the study.

Asthma was diagnosed both by history and clinical examination and by the presence at inclusion of reversible airway obstruction, defined as an increase of FEV_1 by $\geq$ 12% 15 min after inhalation of salbutamol 400 μg per spacer. Patients were divided into 3 subgroups: mild, moderate and persistent asthma (GINA 2005).

We excluded patients with doctor diagnosed acute or chronic inflammatory diseases or with autoimmune diseases and also patients with increased serum C reactive protein, with increased fractions of α2, β or γ globulins at protein electrophoresis, with cryoglobulins or with positive autoimmunity screen panel testing. Churg—Strauss syndrome was excluded if the all following were present: normal chest radiograph, absence of ANCA antibodies and no signs of systemic involvement (mono- or polyneuropathy, skin lesions, muscular or joint symptoms, fever).

Asthma patients included were evaluated at baseline for:

- Demographic features (age, sex)
- Smoking status (history)
- General and pulmonary clinical examination, including height, weight and body mass index
- Atopic status (at least one skin-prick test positive from the common aeroallergens tested: house dust mites, cat, dog, molds, cockroaches, grass pollen, trees pollen, weeds pollen; positive skin-prick test if wheal diameter of allergen/wheal diameter of histamine $>$ 1 and a mean wheal size $\geq$ 3 mm)
- Asthma duration, treatment and severity (GINA 2005 criteria for mild/moderate/severe persistent asthma)
- Lung function (ERS/ATS guidelines): FEV_1 with reversibility testing 15 min after a bronchodilator; FEF 25—75 and MEF50 as indicators of small airway obstruction
- Presence of co-morbidities: non-steroidal anti-inflammatory drugs intolerance (history), moderate/severe persistent rhinitis (as defined by the ARIA document) or chronic rhinosinusitis (confirmed by an ENT specialist), obesity (body mass index $>$25)
- Blood eosinophils and neutrophils; eosinophilia defined as $>$ 4% eosinophils at the differential cell count
- Serum IL-17A and TNF-α: IL-17A was measured using a third generation ELISA (reagent provided by DRG Diagnostics). The cut-off value was set at 20 pg/ml, close to median values for serum IL-17A identified in a previous study in allergic asthma.[12] TNF-α was measured using a chemiluminescent technique (reagent provided by Immulite®). The cut-off value was set at 8.2 pg/ml, as recommended by the manufacturer. We measured both IL-17A and TNF-α since they both promote systemic inflammation and could be correlated or act independently

At least 4 weeks separated the end of an asthma exacerbation and patient baseline evaluation. No systemic anti-inflammatory treatment was allowed for at least 4 least weeks before baseline evaluation.

A control group of 11 atopics non-asthmatics, mean age 33.73 $\pm$ 13.18years old, 27.3% females, was used to compare the IL-17A serum levels with the values measured in asthmatic subjects.

Main outcomes

Serum IL-17A and TNF-α in relation with asthma severity
Serum IL-17 and TNF-α were measured at inclusion and compared between mild, moderate and persistent asthma patients.

Risk factors for severe asthma
The following risk factors for severe asthma were considered in the multiple regression analysis: moderate/severe persistent rhinitis/chronic rhinosinusitis, smoker, obesity, non-steroidal anti-inflammatory drugs intolerance, blood eosinophilia, FEV_1 at baseline $< 50\%$ predicted (low FEV_1), atopic status, and serum IL-17A > 20 pg/ml.

Asthmatic phenotypes in relation with increased serum IL-17
We tested if increased serum IL-17A (>20 pg/ml) is correlated with other phenotypic features of asthma such as associated atopy, non-steroidal anti-inflammatory drugs intolerance, moderate/severe persistent rhinitis/chronic rhinosinusitis, smoker, obesity, FEV_1 at baseline $< 50\%$ predicted, small airways obstruction, blood eosinophilia and neutrophilia, increased serum TNF-α.

Analysis of the subgroup of severe asthma patients
For the subgroup of severe asthma we compared patients with increased serum values of IL-17A with patients with normal serum IL-17A for: demographic characteristics, lung function, mean asthma duration, asthma regular treatment and for risk factors for severe asthma mentioned above.

Data analysis

Data are presented as median (range) values unless otherwise stated. All data were analyzed with STATISTICA 7. The differences between mild, moderate and severe persistent asthma group (Table 1) were tested using the *T*-test for independent samples. The analysis of the differences in medium IL-17A serum concentration between patients with mild, moderate or severe asthma and for the number of patients with IL-17A > 20 pg/ml in each asthma severity group used the *T*-test for independent samples. Risk factors for severe asthma evolution were tested in the multiple linear regression. Correlations between increased serum IL-17A and other phenotypic features of asthma were evaluated using the Pearson correlation test. For the analysis of the subgroup of severe asthma patients features we used both *T*-test and Chi-test. To avoid falsely positive conclusions, the significance level at each test was set to 0.05.

Results

From the initial 127 asthma patients consenting to participate into the study, 85 subjects were selected, after excluding patients with concomitant acute or chronic inflammatory diseases or with autoimmune diseases.

Subject characterisation

Mean age of asthma patients was 46.99 ± 14.1 years (limits 15—73 years old) and 52 (61.18%) were females. All subjects were Caucasians, with no ethnic differences. Mean asthma duration was 12.64 ± 1.19 years (limits 0.58—50 years).

According to GINA criteria 23 (27.06%) patients had mild persistent asthma, 26 (30.59%) moderate persistent asthma and 36 (42.35%) severe persistent asthma.

Patients with severe persistent asthma were significantly ($p = 0.005329$) older (mean age 50.83 ± 2.08 years) compared to mild asthma patients (mean age 41.39 ± 2.44years) and asthma duration was significantly

Table 1 Characteristics of persistent asthma patients at inclusion.

		Mild asthma 23 patients	Moderate asthma 26 patients	Severe asthma 36 patients
Age (years)	mean	41.39 ± 2.44	46.62 ± 3.27	50.83 ± 2.08*
	range	17—63	15—69	24—73
Sex ratio (% females)		73.91%	53.85%	58.33%
Asthma duration (years)	mean	9.26 ± 1.90	9.30 ± 1.59	17.19 ± 2.08**
	range	0.58—34	1—38	2.5—50
FEV_1% predicted	mean	93.74 ± 1.87	80.42 ± 2.38***	61.06 ± 2.68**
	range	79—110	59—100	26—107
Number of eosinophils ($cells/mm^3$)	mean	281.35 ± 36.72	399.19 ± 57.12	396.17 ± 49.52
	range	30—648	70—1228	100—1280
Eosinophils (%)	mean	3.92 ± 0.50	5.31 ± 0.77	4.96 ± 0.65
	range	0.15—8.50	0.20—16.60	0.10—16.20
Asthma treatment	ICS	6(26.09%)	5(19.23%)	4(11.11%)
	ICS + LABA	3(13.04%)	12(46.15%)	23(63.89%)
	ICS + LTRA	0	6(23.08%)	1(2.78%)
	ICS + LABA + LTRA	0		8(22.22%)
	LTRA	14(60.87%)	3(11.53%)	0
	ICS > 1500 μg/day alone or in combination with LABA/LTRA	0	0	25(69.44%)
	No treatment	0	0	0

*$p < 0.05$ severe vs. mild asthma; **$p < 0.05$ severe vs. mild and vs. moderate asthma; ***$p < 0.05$ mild vs. moderate asthma; ICS = Inhaled steroids; LABA = long acting beta 2 agonists; LTRA = leucotriene receptors antagonists.

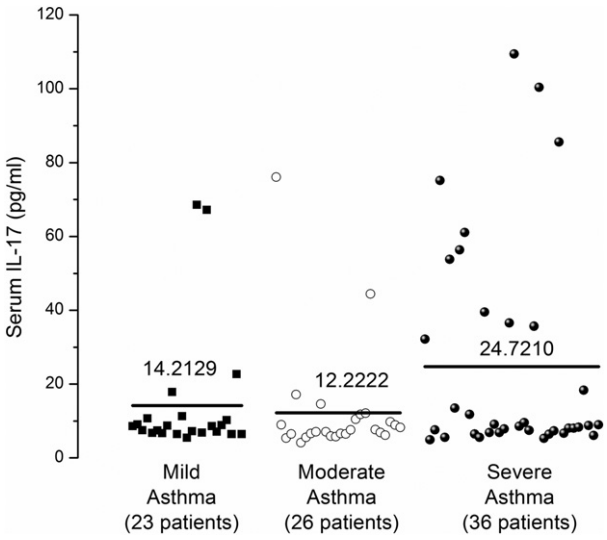

Figure 1 Mean serum IL-17 levels in study groups.

($p = 0.010991$, respective $p = 0.006513$) longer in severe asthma patients (17.19 ± 2.08 years) compared to moderate (9.304 ± 8.12 years) and milder forms of the disease (9.26 ± 1.9 years). Sex ratio was not significantly different between severity groups. FEV_1 was significantly in severe asthma patients compared to the mild ($p = 4.56 \times 10^{-12}$) and moderate asthma ($p = 0.000003$) patients groups, and significantly lower in the moderate asthma patients compared to mild asthma group ($p = 0.000091$) (Table 1). Asthma treatment at inclusion is also described in Table 1.

Serum IL-17 and TNF-α values

In the control group of atopic non-asthmatics mean serum IL-17A was 8.748 ± 11.657 pg/ml, highest value was 33.483 pg/ml. Serum IL-17A was below the detection threshold in 2 cases.

In the asthma patients group highest serum IL-17A value was 109.469 pg/ml, lowest value 4.921 pg/ml. IL-17A values > 20 pg/ml were encountered in 16 patients: 3(13.04%) mild asthma patients ($p < 0.001$ vs. severe asthma), 2(7.69%) moderate asthma patients ($p < 0.001$ vs. severe asthma), and in 11(30.56%) severe asthma patients. IL-17 A values > 100 pg/ml were encountered in 2 patients with severe persistent asthma. Mean serum IL-17 values were 14.21 ± 3.62 pg/ml in mild asthma, 12.22 ± 3.71 pg/ml in moderate asthma and 24.72 ± 4.87 pg/ml in severe asthma (Fig. 1).

Highest serum TNF-α value was 37.7 pg/ml, lowest value 4 pg/ml. TNF-α values > 8.2 pg/ml were encountered in 55 patients: 13(56.52%) mild asthma patients, 18(69.23%) moderate asthma patients and in 24(66.67%) severe asthma patients. Mean serum TNF-α values were 8.88 ± 0.6 pg/ml in mild asthma, 11.31 ± 1.5 pg/ml in moderate asthma and 12.02 ± 1.17 pg/ml in severe asthma.

Risk factors for severe asthma

Increased serum IL-17 (>20 pg/ml) was tested in the multiple regression analysis model as risk factor for severe asthma in comparison with ''traditional'' risk factors: smoker, non-steroidal anti-inflammatory drugs intolerance, obesity, moderate/severe persistent rhinitis or chronic rhinosinusitis, blood eosinophilia, FEV_1 at baseline < 50% predicted (low FEV_1). The incidence of analyzed risk factors is displayed in Table 2.

For severe asthma multiple regression analysis revealed as independent risk factors IL-17 > 20 pg/ml, ($p = 0.000257$), non-steroidal anti-inflammatory drugs intolerance ($p = 0.000649$) and low FEV_1 ($p = 0.000043$) (Table 3).

Correlations between increased serum IL-17 and other phenotypic features of asthma

Serum IL-17 > 20 pg/ml was negatively correlated with increased blood neutrophils ($r = -0.3376$, $p = 0.047$) and with small airways obstruction ($r = -0.4526$, $p = 0.006$) and was not correlated with the presence of atopy, blood eosinophilia, smoker, obesity, moderate/severe persistent rhinitis or chronic rhinosinusitis, non-steroidal anti-inflammatory drugs intolerance, FEV_1 < 50% predicted or increased serum TNF-α (Table 4).

Table 2 Incidence of risk factors for severe asthma in study subgroups.

Risk factor	Incidence in the mild asthma group (23 subjects)	Incidence in the moderate asthma group (26 subjects)	Incidence in the severe asthma group (36 subjects)
Smoke	9(20.7%)	11(42.31%)	13 (36.11%)
NSAID intolerance	4(17.39%)	9(34.61%)	24(66.67%)
Atopy	14(60.87%)	11(42.31%)	13 (36.11%)
Obesity	12(52.17%)	14(53.85%)	26(30.59%)
Moderate/severe persistent rhinitis/chronic rhinosinusitis	21(91.3%)	21(80.77%)	32(88.89%)
Blood eosinophilia	10(43.48%)	15(57.69%)	14(38.89%)
FEV_1 < 50% predicted	0	0	11 (30.56%)
Age>50 years old	7(30.43%)	12(46.15%)	22(61.11%)
Asthma duration > 5 years	22(95.65%)	25(96.15%)	26(100%)
IL-17 > 20 pg/ml	3(13.04%)	2(7.69%)	11 (30.56%)

NSAID = non-steroidal anti-inflammatory drugs.

Table 3 Risk factors for severe asthma in the multiple regression analysis model.

	Beta	Standard Error of Beta	B	Standard Error of B	t(73)	p-level
Smoke	0.010273	0.092371	0.010370	0.093245	0.11121	0.911746
NSAID intolerance	0.346923	0.097467	0.345615	0.097099	3.55940	0.000649
Atopy	−0.076304	0.098527	−0.075581	0.097593	−0.77445	0.441099
Obesity	−0.002673	0.104863	−0.002714	0.106457	−0.02549	0.979728
Moderate/severe persistent rhinitis/chronic rhinosinusitis	−0.028323	0.097938	−0.041392	0.143129	−0.28919	0.773233
Blood eosinophilia	−0.094935	0.093798	−0.093847	0.092722	−1.01213	0.314731
$FEV_1 < 50\%$ predicted	0.400498	0.092198	0.609701	0.140359	4.34388	0.000043
IL-17 > 20 pg/ml	0.352762	0.091920	0.442894	0.115406	3.83770	0.000257

NSAID = non-steroidal anti-inflammatory drugs.

Analysis of the subgroup of patients with severe asthma

Compared to severe asthma patients with normal values of IL-17A versus those with severe asthma and IL-17A > 20 pg/ml there was significantly lower incidence of smokers ($p = 0.0005$), of subjects >50 years old ($p = 0.0002$) and of non-steroidal anti-inflammatory drugs intolerance ($p = 0.0010$) and significantly higher incidence of eosinophilia ($p = 0.0471$), atopy (0.0025) and preserved lung function ($p = 0.0000$) (Table 5).

Discussion

No data exist on serum IL-17 in asthma, most of the studies concentrated on measuring IL-17 in sputum or bronchial biopsies. We chose serum IL-17 as an indicator for severe asthma because it is easily measurable compared to its determination in induced sputum, broncho-alveolar lavage or bronchial biopsies. Our study demonstrates that it can be use to predict asthma severity since it is both increased in severe asthma compared to mild/moderate forms of the disease and is an independent predictor of severe asthma. The results are in concordance with other studies underlying the link between systemic inflammation and asthma severity.[9,10] Also, a trend towards increased production of IL-17 was reported for another phenotype of severe asthma, Churg—Strauss syndrome.[13]

Increased serum IL-17 was more discriminative for severe asthma compared to serum TNF-α. Also, there was no correlation between increased serum IL-17 and serum TNF-α, thus both depicting separate phenotypes of asthma.

Although median values of serum IL-17 were not discriminative for severe asthma compared to mild/moderate forms of the disease, there were significantly more asthma patients with values above 20 pg/ml in the severe asthma group compared to mild or moderate asthma patients. Very high values for serum IL-17 (>100 pg/ml) were encountered only in the severe asthma patient's subgroup. The dissociation between mean values and individual values underlines the heterogeneity of severe asthma, with increased serum IL-17 more relevant for a subphenotype of severe asthma, non-smokers, without non-steroidal anti-inflammatory drugs intolerance, with preserved lung function and with normal serum TNF-α.

The cross-sectional nature of the study may dampen the resulting prognostic value of increased serum IL-17 for severe asthma. None-the-less, many validated parameters that we actually use for predicting asthma severity came first from cross-sectional studies, using the same methodology that we used.[14,15] Validation of serum IL-17 in a prospective cohort of severe asthma patients is however warranted.

Patients with severe persistent asthma were significantly older compared to mild asthma patients and there are relevant differences between study groups in term of treatment. Also, the control group of atopics non-asthmatics were younger and had less females compared to the study groups. These demographic differences should be taken into account when interpreting the main outcomes of the study.

The inverse correlation with blood neutrophils is surprising, since most of the studies associate IL-17 with neutrophilic inflammation.[1,4] The association in this case may be true for lung inflammation and the decreased blood neutrophils may reflect their recruitment into the lungs.

The relation between increased serum IL-17 and lung function is interesting. There was an inverse correlation with small airways obstruction (as evaluated by FEF 25—75 and MEF50) and there is also a tendency towards inverse relation, although not statistically significant, with low lung

Table 4 Correlation between increased serum IL-17 and other phenotypic features of asthma.

Parameter	Coefficient	*p* value
Atopic status	0.1290	0.453
Moderate/severe persistent rhinitis or chronic rhinosinusitis	0.2345	0.169
Smoke	−0.1221	0.478
Obesity	0.0075	0.965
NSAID intolerance	−0.1706	0.320
$FEV_1 < 50\%$ predicted	−0.3091	0.067
Small airways obstruction	−0.4526	0.006
Blood eosinophilia	0.0210	0.247
Blood neutrophilia	−0.3376	0.047
TNF-α>8.2 pg/ml	0.0606	0.729

NSAID = non-steroidal anti-inflammatory drugs.

Table 5 Characterisation of severe asthma patients with high levels of serum IL-17 (>20 pg/ml).

		Serum IL-17 > 20 pg/ml (11 subjects)	Serum IL-17 < 20 pg/ml (25 subjects)
Age (years)	mean	47.64 ± 4.04	52.24 ± 2.42
	range	24–63	26–73
Sex ratio (% females)		72.73%	52%
Asthma duration (years)	mean	14.29 ± 3.58	18.47 ± 2.55
	range	3–40	2.5–50
Asthma treatment	ICS	3 (27.3%)	1(4%)
	ICS + LABA	5(45.5%)	18(72%)
	ICS + LTRA	1(9.1%)	0
	ICS + LABA + LTRA	2(18.2%)	6(24%)
	ICS > 1500 μg/day alone or in combination with LABA/LTRA	6(54.5%)	19(76%)
FEV_1 % predicted	mean	72.73 ± 4.60*	55.92 ± 13.79
	range	48–107	26–78
Number of eosinophils ($cells/mm^3$)	mean	551.82 ± 102.36*	324.83 ± 244.69
	range	200–1280	100–1000
Eosinophils (%)	mean	7.26 ± 1.40*	3.90 ± 2.95
	range	2–16.20	0.10–11.80
Smoke		3(27.3%)**	10(40%)
NSAID intolerance		6(54.5%)**	18(72%)
Atopy		5(45.5%)**	8(32%)
Obesity		9(81.8%)	17(68%)
Moderate/severe persistent rhinitis/chronic rhinosinusitis		11(100%)	21(84%)
Blood eosinophilia		6(54.5%)**	8(32%)
FEV_1 < 50% predicted		1(9.1%)**	10(40%)
Age>50 years old		5(45.5%)**	17(68%)
Asthma duration > 5 years		8(72.7%)	18(72%)

T-test: *$p < 0.05$; Chi-test: **$p < 0.05$.

function as depicted by an FEV_1 value below 50% predicted. In the analysis of severe asthma patients subgroup FEV_1 % predicted was significantly higher and the number of subjects with FEV_1 <50% significantly lower in association with increased serum levels of IL-17A. It seems that IL-17 is increased in subgroup of severe asthma patients with more preserved lung function. In another study sputum IL-17 was associated with increased bronchial hyperreactivity to methacholine.[7] Increased IL-17 may thus characterise a peculiar lung remodeling with increased bronchial smooth muscle and less fibrosis.

There is also a tendency for an inverse relationship between smoking and increased serum IL-17 and the incidence of smokers is significantly lower in severe asthma patients with increased serum IL-17 compared to severe asthmatics with normal values of IL-17A. It may seem that increased serum IL-17 is more powerful as a risk factor in non-smoking asthma patients. The same pattern (tendency towards an inverse relationship and decreased incidence in severe asthmatics with high serum IL-17) can be observed for increased serum IL-17 and non-steroidal anti-inflammatory drugs intolerance. It may also be true that increased serum IL-17 may be more valuable in severe asthma patients without non-steroidal anti-inflammatory drugs intolerance.

Inhaled steroids, even at high concentrations (>1500 μg/day) did not influence serum values of IL-17. The effect of systemic steroids is unknown since per protocol the evaluation was done at least 4 weeks after an asthma exacerbation resolution.

There are no data correlating sputum/bronchial biopsies IL-17 with serum IL-17. Since both were demonstrated to be increased in severe asthma, a study evaluating the link between local (pulmonary) and systemic (serum) IL-17 is more than appropriate and desired.

In conclusion serum IL-17 is increased in a subgroup of patients with severe asthma compared to mild/moderate forms of the disease and values above 20 pg/ml are an independent risk factor for severe asthma. Also, increased serum IL-17 did not correlate with other phenotypic features of asthma (atopy, blood eosinophilia, smoker, obesity, non-steroidal anti-inflammatory drugs intolerance, moderate/severe persistent rhinitis or chronic rhinosinusitis, FEV_1 < 50% predicted, increased serum TNF-α) and thus could depict a special subphenotype of severe asthma.

Conflict of interest

None.

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