Subtypes of Severe Asthma Based on A Combination of Blood Eosinophil Counts and Levels of Exhaled Nitric Oxide

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Rationale

1) Patients with severe asthma (SA) has been provided with clinical benefit according to classification based on blood eosinophil counts (bl-Eos).

Blood eosinophil ≧400/μL is likely

- ✓ a risk factor of severe exacerbation. : adjusted RR 1.31 (Zeiger RS, et al. JACI Pract 2014;2:741-50)
- ✓ a predictive marker of sputum eosinophilia. (Fowler SJ, et al. JACI 2015;136:822-24)

2) Exhaled nitric oxide (FENO) is a major predictive marker for eosinophilic airway inflammation. High levels of FENO also seem to represent Type 2 airway inflammation because of their production by IL-4/-13.

- ✓ FENO is recognized as a surrogate marker of eosinophilic airway inflammation. (Dweik RA, et al. AJRCCM. 2011;184:602-15.)

Objective

The objective of this study is to address phenotypes of severe eosinophilic asthma based on the classification by the combination of FENO as a biomarker of type 2 airway inflammation and b-Eos as a biomarker of potent systemic eosinophilic inflammation.

Methods

Subjects

Eligible patients were :

1) ≥ 20 years old coming to our outpatient clinic section.
2) Diagnosed as severe asthma based on Japanese guidelines for adult asthma 2017 (Allergol Int. 2017;66:163-189).

Methods

1) A cross-sectional observational study
2) The data was extracted from outpatient medical record for a year beginning from the day bloods were obtained.

Measurements

- ✓ Medical record: age, sex, BMI, smoking history, sensitization to allergens, allergic comorbidities, medication, acute exacerbation history
- ✓ Blood: b-Eos, total IgE, FENO, Pulmonary function

Classification

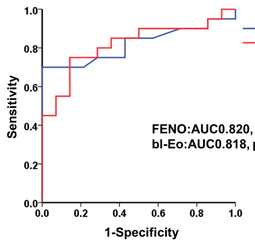
Eligible patients were divided into 4 subgroups defined by the following cutoffs for FENO values (ppb) and bl-Eos counts (cells/mm^3).

- ✓ Low FENO and low bl-Eos: FENO < 38 and bl-Eos < 300
- ✓ High FENO and low bl-Eos: FENO ≥ 38 and bl-Eos < 300
- ✓ Low FENO and high bl-Eos: FENO < 38 and bl-Eos ≥ 300
- ✓ High FENO and high bl-Eos: FENO ≥ 38 and bl-Eos ≥ 300

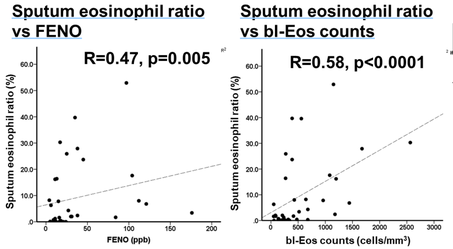
Cutoff values were decided by identifying the optimal cut-off value for sputum eosinophils ≥ 3% with the use of receiver operating characteristic curve (ROC) analysis.

The optimal cut-off values of FENO and bl-Eos for sputum eosinophil ratios ≥ 3%

The ROC for individual FENO values and bl-Eos counts to differentiate between sputum eosinophil <3% and ≥3%



Correlation of sputum eosinophil ratios with FENO and bl-Eos counts



Dicision of the cut-off values of FENO and bl-EOS

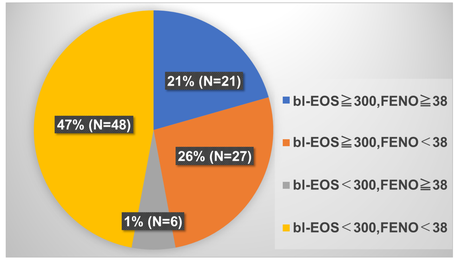
		Sensitivity	Specificity
FENO	37	45.0%	100%
(ppb)	42	35.0%	100%
bl-Eos	296	75.0%	71.4%
(/μL)	330	75.0%	79.6%

The optimal cut-off values
FENO 38ppb
Bl-Eos 300/μL

Demographic of SAs

	All subjects (n=102)	Subjects with induction sputum (n=36)
Female/male, n	59 / 43	23/13
Age, y, Median (IQ)	64 (51 - 73)	60 (46-75)
BMI, kg/m^2 (IQ)	23.3 (21.4 – 25.8)	25.0 (19.5-30)
Smokers, n (%)	18(27.2)	5 (13.9)
Duration, m, Median (IQ)	154 8 (66.3 – 303.8)	115
Allergic rhinitis, n (%)	63 (61.2)	24 (66.7)
Sinusitis, n (%)	19 (18.4)	8 (22.2)
Atopic dermatitis, n (%)	45 (43.7)	13 (36.1)
ICS dose, μg/d, Median (IQ)	1000 (800 – 1200)	983 (617-1349)
Oral corticosteroid, n (%)	38 (29.1)	8 (22)
Anti-IgE, n (%)	10 (9.7)	4 (11.1)
%FEV1, (%)	85.2±24.9	72±20.5
FEV1/FVC, (%)	70.0±15.0	67.9±14.8
Sputum eosinophil ratio (%)	-	2.2 (0.3-16.4)
Sputum neutrophil ratio (%)	-	34.9 (15.0-64.7)

Distribution of SAs classified by bl-EOS and FENO



Annual acute exacerbations

	FENO < 38, bl-Eos < 300 (N = 48)	FENO ≥ 38, bl-Eos < 300 (N= 6)	FENO < 38, bl-Eos ≥ 300 (N = 27)	FENO ≥ 38, bl-Eos ≥ 300 (N = 21)	P value
Annual acute exacerbations, times/person					
Mild to moderate	0.9 (0.4 - 1.4)	0.8 (0.0 – 1.6)	0.8 (0.3 – 1.3)	1.5 (0.8 – 2.1)	N.S.
Severe	0.9 (0.6 - 1.3)	1.2 (0.1 – 2.2)	1.5 (0.8 – 2.2)	2.3 (1.3 – 3.2)	0.009
Total	1.8 (1.1-2.5)	2.0 (0.3 – 3.6)	2.3 (1.4 – 3.2)	3.8 (2.6-5.0)	0.02

Exacerbation classifications (NIH,EPR-3 guideline published in 2007)

Clinical biomarkers

	FENO < 38, bl-Eos < 300 (N = 48)	FENO ≥ 38, bl-Eos < 300 (N= 6)	FENO < 38, bl-Eos ≥ 300 (N = 27)	FENO ≥ 38, bl-Eos ≥ 300 (N = 21)	P value
Blood Eosinophil. (/μL)	143±11	175±105	578±459	738±352	<0.001
FENO (ppb)	16 (13 - 19)	62 (42 - 82)	20 (17 - 23)	71 (56 - 87)	< 0.001
Log IgE	2.2±0.6	2.2±1.1	2.2±0.6	2.4 ± 0.5	N.S.
FEV1 (L)	2.0±0.7	1.7±0.6	1.8±0.7	1.7±0.4	N.S.
%FEV1 (%)	87.7±23.0	108±29.6	82.9±21.0	79.8±23.0	N.S.
FVC (L)	3.0±0.8	2.4±0.5	2.5±0.7	2.7±0.6	0.045
%FVC (%)	98.1±23.0	113±15.2	88.9±21.6	89.6±21.5	0.042
FEV1/FVC (%)	68.7±16.9	67.4±13.7	70.0±13.9	64.1±11.9	N.S.
Sputum	(N= 16)	(N= 0)	(N= 10)	(N= 10)	
Eosinophil (%)	1.0 (0.0 – 2.0)	–	6.1 (0.4 – 19.7)	12.8 (3.2 – 30.8)	0.005
Neutrophil. (%)	24.3 (12.7 – 77.5)	–	42.0 (16.1 – 90.0)	35.2 (24.6 – 60.5)	N.S.

Conclusions

- ✓ The classifications of SA based on airway and systemic type 2 inflammation biomarker demonstrated features of SAs.
- ✓ SAs with high FENO and b-Eos exhibited frequent severe asthma exacerbations, higher prevalence of chronic sinusitis and lower %FVC.
- ✓ SAs with high FENO or b-Eos exhibited a few severe asthma exacerbations and higher prevalence of chronic sinusitis.
- ✓ SAs with both high type 2 inflammation biomarkers are consistently under unstable condition despite of guideline therapy.

COI Disclosure
Name of first author: Hidetoshi Iemura
The presenters have no financial conflicts of interest to disclose concerning the presentation.