ORIGINAL ARTICLE

Relevance of T_H2 Markers in the Assessment and Therapeutic Management of Severe Allergic Asthma: A Real-Life Perspective

Caminati M[1], Vianello A[2], Chieco Bianchi F[2], Festi G[3], Guarnieri G[4], Marchi MR[2], Micheletto C[5], Olivieri M[6], Tognella S[7], Guerriero M[8], Senna G[1], on behalf of the NEONET Study Group*

[1]Asthma Center and Allergy Unit, Verona University Hospital, Verona, Italy
[2]Respiratory Pathophysiology Division, University-City Hospital of Padua, Padua, Italy
[3]Pulmonary Unit, Verona University Hospital, Verona, Italy
[4]Department of Cardiologic, Thoracic and Vascular Sciences, University of Padua, Padua, Italy
[5]Respiratory Unit, Mater Salutis Hospital, Legnago, Italy
[6]Unit of Occupational Medicine, Verona University Hospital, Verona, Italy
[7]Respiratory Unit, Orlandi General Hospital, Bussolengo, Italy
[8]Department of Computer Science, University of Verona, Verona, Italy

*Denise Artioli, Elisabetta Bertocco, Lucio Bonazza, Mariangiola Crivellaro, Fabio De Conti, Annarita Dama, Giulio Donazzan, Giuseppe Idotta, Carlo Lombardi, Luigi Marino, Francesco Mazza, Stefano Nardini, Federico Reccardini, Michele Schiappoli.

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Abstract

Background: Although blood eosinophils are currently recognized as the main clinical marker of T_H2-type inflammation, their relevance in identifying asthma severity remains a matter of debate.
Methods: Our retrospective real-life study on severe asthmatics included in the NEONet Italian database aimed to investigate the relevance of blood eosinophil count and fractional exhaled nitric oxide (FeNO) in the clinical assessment of severe asthma and their role as potential predictors of responsiveness to anti-IgE therapy. The cut-off values chosen were 300 eosinophils/mm^3 and FeNO of 30 ppm.
Results: We evaluated 132 adult patients. No significant differences were observed between the groups (high and low baseline eosinophil counts) in terms of demographic data, total IgE, lung function, patient-reported outcomes, or nasal comorbidities. The Asthma Control Test score and Asthma Quality of Life Questionnaire scores were poorer in patients with FeNO ≥30 ppb than in patients with FeNO <30 ppb. In the high FeNO subgroup, more frequent hospital admissions and a higher number of working days lost in the previous year were registered. A combined score including both eosinophils and FeNO did not improve the accuracy of the individual parameters. In the high-eosinophil subgroup, the proportion of responders to omalizumab was greater and increased at each follow-up time point.
Conclusions: Our findings show that blood eosinophil count is not an unequivocal marker of asthma severity, whereas a higher FeNO level is associated with more frequent hospital admissions and more working days lost. Blood eosinophils seem to act as a predictor of response to omalizumab.

Key words: Severe asthma. Eosinophils. Omalizumab. Biomarker. T_H2 inflammation. Asthma network.

Resumen

Antecedentes: Aunque los eosinófilos en la sangre actualmente son reconocidos como el principal marcador clínico de la inflamación Th2, su relevancia en la identificación de la gravedad del asma sigue siendo un tema de debate.
Métodos: Nuestro estudio retrospectivo de la vida real sobre asmáticos graves, incluido en la base de datos italiana de NEONet, tuvo como objetivo investigar la relevancia del recuento de eosinófilos en sangre y el FeNO en la evaluación clínica del asma grave y su función como posible factor predictivo de la capacidad de respuesta al tratamiento con anti-IgE. Como valores de corte se eligieron 300 eosinófilos/mm^3 en sangre y 30 ppm para FeNO.
Resultados: En total se evaluaron 132 pacientes adultos. No se pudieron observar diferencias significativas entre los grupos de eosinófilos basales altos y bajos, en términos de datos demográficos, IgE total, función pulmonar, resultados informados por el paciente (PRO) o comorbilidades nasales. Los pacientes con ≥ FeNO 30 ppb mostraron una puntuación de ACT peor y una puntuación AQLQ más baja en comparación con los de FeNO <30 ppb. En el subgrupo de FeNO alto, se registraron ingresos hospitalarios con más frecuencia y un mayor número de días de trabajo perdidos en el último año. Una puntuación combinada que incluye tanto a los eosinófilos como el FeNO no mejoró la precisión de los parámetros individuales. En el subgrupo de eosinófilos altos, la proporción de pacientes que respondieron al tratamiento con omalizumab fue mayor y aumentó significativamente en cada punto de tiempo de seguimiento.

Conclusiones: De acuerdo con nuestros hallazgos, los eosinófilos en sangre no representan un marcador unívoco de la gravedad del asma, mientras que un nivel más alto de FeNO se asocia con más ingresos hospitalarios y más días de trabajo perdidos. Los eosinófilos de la sangre parecen actuar como predictores de la respuesta del tratamiento al omalizumab.

Palabras clave: Asma grave. Eosinófilos. Omalizumab. Biomarcador. Inflamación TH2. Red de asma.

Introduction

According to recent studies, eosinophils play a crucial role in the pathogenesis and clinical management of asthma. In fact, eosinophils characterize the type 2 asthma phenotypes, including early-onset atopic asthma and late-onset asthma with nasal polyps [1]. Furthermore, a high blood eosinophil count is predictive of increased eosinophilic inflammation in sputum [2,3]. In clinical terms, the blood eosinophil count was recently identified as a reliable biomarker in the selection of candidates for biological treatments [4-11]. Fractional exhaled nitric oxide (FeNO) is considered a surrogate of eosinophilic airway inflammation and a good marker of eosinophilic bronchial inflammation and, albeit to a lesser extent, of blood eosinophilia [12]. Day-to-day management of asthma increasingly requires biological markers that are related to the severity of the disease or that are able to predict it [13]. However, before such biomarkers can be widely used, they must be shown to be feasible, specific, quickly measured, and inexpensive. We carried out a real-life study in a population of patients with severe allergic asthma according to European Respiratory Society/American Thoracic Society criteria [14] who were selected for treatment with omalizumab. We investigated the relevance of well-known clinical biomarkers of T_H2-type inflammation (blood eosinophil count and FeNO) in the framework of severe asthma and assessed their correlation with clinical and functional parameters at baseline. Furthermore, we evaluated the role of baseline eosinophil level as a potential predictor of responsiveness to treatment (evaluation at 6, 12, and 18 months of follow-up).

Material and Methods

A retrospective analysis of the North East Omalizumab Network (NEONet) database was carried out. A detailed description of the Network in terms of aims and methods is provided elsewhere [15]. In brief, NEONet is a nonprofit initiative involving 19 allergy and respiratory referral centers for severe asthma located in the northeast region of Italy. Use of the database was approved by the local ethics committee. NEONet aims to provide real-word evidence by collecting homogeneous clinical data from adult patients affected by severe allergic asthma and undergoing treatment with omalizumab in a real-life setting in order to generate new insights concerning currently unmet needs (eg, impact of omalizumab on lung function and comorbidities of asthma, long-term follow-up of treated patients, adherence, nonresponder profile, optimal treatment duration). Once informed consent is obtained from the patients, the participating clinicians enter anonymous coded data into a shared limited-access web platform. In the present study, we analyzed clinical data, lung function, blood eosinophil count, and FeNO levels registered at the enrolment visit. The sensitization profile was also assessed by measuring total and specific IgE in blood. In order to cluster patients with more pronounced eosinophilic inflammation, the cut-offs chosen were 300 eosinophils/mm^3 and 30 ppm (FeNO) [16]. Omalizumab doses and treatment schedule were established according to the criteria of the Agenzia Italiana del Farmaco (Italian Drug Regulatory Agency) [17]. Blood eosinophil count was monitored at 6, 12, and 18 months and matched with the evaluation of response to treatment (assessed at the same time points). Response to treatment was evaluated based on the Global Evaluation of Treatment Efficacy (GETE) [18]. GETE uses a 5-point scale including 5 possible outcomes: excellent (complete control of asthma), good (marked improvement), moderate (discernible but limited improvement), poor (no appreciable change), and worsening. According to the rating of symptom control, the patients were classified as responders (excellent/good) or nonresponders (moderate/poor).

Statistical Analysis

Results are expressed as mean (SD) for continuous variables and as a percentage for categorical variables. The Shapiro-Wilk test was used to test the normality for continuous variables. The 2-sample *t* test or the Wilcoxon (Mann-Whitney) rank-sum test was used to compare the mean of continuous variables, whereas analysis of variance or the Kruskal-Wallis rank test was used when the mean comparison involved more than 2 independent groups. A P value <.05 was considered to be statistically significant. The analyses were performed using STATA version 15 (StataCorp).

Results

The population sample included 151 adult patients. Nineteen were excluded, as they were receiving oral corticosteroids at enrolment and measurement of the eosinophil count. The analysis was therefore based on 132 patients. As previously mentioned, all the patients included had been selected for treatment with omalizumab and were receiving a Global Initiative for Asthma (GINA) step 5 treatment. All patients were on regular treatment with a combination of inhaled corticosteroids (mean [SD] dose, 1080.5 [487.3] mg of fluticasone propionate equivalents) plus long-acting β-agonists. Pharmacological treatment also included a leukotriene receptor antagonist in 41.7% of patients and a long-acting muscarinic antagonist in 39.4%. Demographic data are summarized in Table 1.

As shown in Table 2, no significant differences were observed at baseline between the high- and low-eosinophil-count groups in terms of demographic data, total IgE, lung function assessment, and patient reported outcomes (PROs). As for nasal comorbidities, rhinitis was slightly more prevalent in the high-eosinophil-count group than in the low-eosinophil-count group (86.8% vs 69.6%, P=.075), whilst nasal polyposis did not reproduce the same trend and was uniformly distributed between the groups. In addition, the average number of working days lost in the previous year was higher in the high-eosinophil-count group than in the low-eosinophil-count group.

Table 3 summarizes the baseline clinical and functional features of patients after dividing the study population according to FeNO values (cut-off, 30 ppb). Significant differences were found between the subgroups in body mass index, which was higher in the low-FeNO group. The percentage of patients taking oral corticosteroids was significantly lower in this group. The Asthma Control Test (ACT) score and Asthma Quality of Life Questionnaire (AQLQ) score were lower in patients with FeNO ≥30 ppb than in those with FeNO <30 ppb. In addition to PROs, asthma control was poorer in the high FeNO subgroup and was characterized by more frequent hospital admissions and more working days lost in the previous year.

As shown in Table 4, a combined score including both eosinophils and FeNO does not seem to improve the accuracy of the individual parameters for identifying the clinical severity of the disease.

According to the GETE questionnaire, the proportion of responders was higher in the high-eosinophil-count subgroup; in the low-eosinophil-count subgroup, the number of nonresponders was high (Figure). Furthermore, within the high-eosinophil-count subgroup, the proportion of responders increased at each follow-up point. This trend was not so evident in the low-eosinophil-count subgroup.

Table 1. Demographic Data[a]

Age, y	46.9 (13.3)
Males, %	44
Current smokers, %	5.7
Pack years	9.4 (12.2)
Years of smoking	11.3 (9.1)
Body mass index	25.5 (5.1)
Total IgE	395.9 (403.9)
Sensitization to aeroallergens, %	100%

[a]Data are shown as mean (SD) unless otherwise indicated.

Discussion

Our real-life study of patients with severe asthma selected for treatment with omalizumab highlighted a poor association between peripheral blood eosinophil count and lung function, FeNO, and PROs. In addition, blood eosinophil count did not seem to be a relevant parameter for detecting a specific

Table 2. Comparison of Patients' Demographic and Clinical Variables in High and Low Baseline Eosinophil Subgroups[a]

	Eosinophil Count, mm^3		
	<300	≥300	*P* Value
Demographic data			
Age	43.7 (12.8)	47.1 (14.8)	.16
Gender, % male	47.8	49.1	.92
Smoking, %	13.0	1.9	.10
Body mass index	25.8 (6.4)	25.4 (4.5)	.40
Total IgE	477.0 (588.0)	360.6 (291.2)	.19
Perennial sensitizations, %	91.3	98.1	.17
History of oral corticosteroids, %	52.2	56.6	.72
Lung function and PROs			
FEV_1, %	69.7 (18.8)	69.9 (17.4)	.48
FVC, %	83.9 (13.4)	84.4 (15.5)	.44
FEV_1/FVC ratio	0.7 (0.1)	0.7 (0.1)	.25
ACT	14.2 (4.3)	14.2 (5.6)	.47
AQLQ	3.7 (1.1)	3.7 (1.4)	.47
FeNO	36.3 (35.8)	47.8 (51.2)	.16
Direct and indirect costs			
Admissions to the ED in the previous year	1.1 (2.3)	0.9 (1.9)	.35
Admissions to hospital in the previous year	0.3 (0.8)	0.4 (0.7)	.31
Unscheduled visits	3.2 (3.2)	3.5 (3.2)	.35
Working days lost in the previous year	13.4 (16.8)	24.7 (43.0)	.07
Nasal comorbidities			
Polyposis, %	26.1	37.7	.32
Rhinitis, %	69.6	86.8	.07

Abbreviations: ACT, asthma control test; AQLQ, asthma quality of life questionnaire; ED, emergency department; PRO, patient-reported outcome.
[a]Values are shown as mean (SD) unless otherwise indicated.

Table 3. Comparison of Patients' Demographic and Clinical Variables in High and Low Baseline FeNO Subgroups

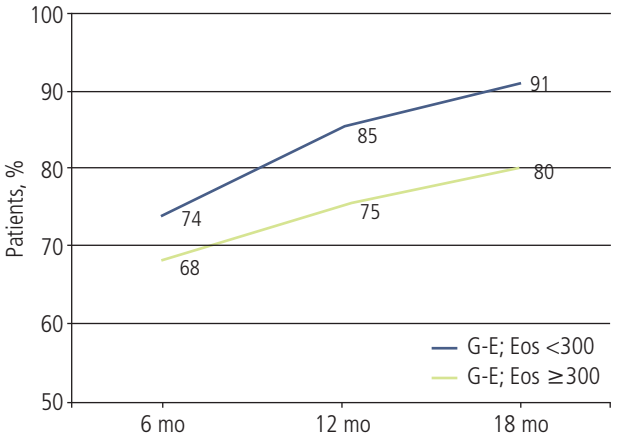
	FeNO, ppb		
	<30	≥30	*P* Value
Demographic data			
Age	45.1 (15.4)	46.1 (11.5)	.37
Male gender, %M	45.8	43.8	.84
Smoking, %	31.3	14.6	.05
Body mass index	26.3 (5.9)	24.1 (4.3)	.02
Total IgE	383.3 (339.1)	359.0 (314.6)	.36
Perennial sensitizations, %	95.7	93.8	.52
History of oral corticosteroids, %	33.3	56.3	.02
Lung function, PROs, and eosinophils			
FEV_1, %	68.0 (15.5)	71.0 (20.5)	.20
FVC, %	83.8 (16.8)	88.9 (17.2)	.07
FEV_1/FVC ratio	0.7 (0.1)	0.7 (0.1)	.16
ACT	15.8 (5.9)	13.7 (5.4)	.04
AQLQ	4.1 (1.4)	3.5 (1.2)	.04
Eosinophils	0.87 (0.27)	0.98 (0.22)	.3803
Direct and indirect costs			
Admissions to the ED in the previous year	1.2 (2.6)	1.3 (2.2)	.41
Admissions to hospital in the previous year	0.3 (0.9)	0.7 (1.0)	.04
Unscheduled visits	3.4 (3.0)	3.6 (3.2)	.39
Working days lost in the previous year	11.8 (15.8)	26.9 (39.9)	.03
Nasal comorbidities			
Polyposis, %	27.1	41.7	.13
Rhinitis, %	68.8	75	.49

Abbreviations: ACT, asthma control test; AQLQ, asthma quality of life questionnaire; ED, emergency department; PRO, patient-reported outcome.
[a]Values are shown as mean (SD) unless otherwise indicated.

Table 4. Comparison of Patients' Demographic and Clinical Variables in Different Subgroups According to a Combined Eosinophils/FeNO Index

	Eosinophil Count, mm^3; FeNO, ppb					
Variable	<300; <30	<300; ≥30	≥300; <30	≥300; ≥30	*P* Value	Bartlett
Demographic data						
Age, y	42.9 (13.7)	42.0 (15.1)	46.1 (16.9)	46.3 (10.3)	.8385	0.213
Male sex, %	61.5	50	47.8	50	.88	--
Smoker, %yes	38.7	33.3	17.4	15	.35	--
Body mass index	27.5/7.4)	21.8 (4.2)	25.6 (4.2)	24.9 (5.3)	.1836	0.12
Total IgE	347.2 (415.2)	613.7 (475.2)	441.6 (338.7)	311.6 (244.7)	.2447	0.132
Perennial sensitizations, %	92.3	83.3	95.7	100	.379	--
History of oral corticosteroids, %	46.2	50	60.9	55	.843	--
Lung function and PROs						
FEV_1, %	63.7 (16.7)	74.7 (15.9)	73.7 (9.4)	66.0 (18.8)	.1563	0.026
FVC, %	78.0 (12.9)	91.7 (8.7)	87.3 (11.1)	84.8 (15.9)	.121	0.271
FEV_1/FVC ratio	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	.2269	0.349
ACT	14.9 (4.4)	13.2 (5.3)	14.9 (6.0)	14.7 (5.9)	.9256	0.72
AQLQ	3.7 (1.2)	3.3 (0.6)	4.0 (1.4)	3.4 (1.4)	.5051	0.509
Direct and indirect costs						
Admission to the ED in the previous year	1.1 (2.9)	1.8 (1.6)	1.0 (2.5)	1.1 (1.6)	.8671	0.088
Admissions to hospital in the previous year	0.25 (0.62)	0.67 (1.2)	0.35 (0.71)	0.55 (0.89)	.6257	0.235
Unscheduled visits	3.5 (4.0)	3.8 (1.5)	3.0 (2.1)	4.1 (4.4)	.7562	0.001
Working days lost in the previous year	16.8 (19.3)	10.0 (7.1)	11.7 (16.2)	36.6 (50.9)	.0975	<0.001
Comorbidities						
Polyposis, %yes	15.4	50	47.8	35	.238	--
Rhinitis, %yes	69.2	100	95.7	90	.078	--

Abbreviations: ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; ED, emergency department; PRO, patient-reported outcome.
[a]Values are shown as mean (SD) unless otherwise indicated.



	≥300 (n=23)	<300 (n=53)	Difference	95%CI (vs difference)	P Value (vs difference)
6 months	74%	68%	6%	-16%;28%	.3003
12 months	85%	75%	10%	-9%;29%	.1667
18 months	91%	80%	11%	-5%;27%	.1186

Figure. Trend for responders (defined by GETE questionnaire) in high and low basal eosinophils subgroups. Eos indicates baseline blood eosinophil level; G, good responder; E, excellent responder.

clinical-anthropometric patient profile in terms of demographic data, total IgE, and nasal comorbidities. FeNO >30 ppb was associated with poorer asthma control as defined by the ACT and AQLQ scores, hospital admissions, and number of working days lost in the previous year. In contrast, omalizumab seemed more likely to be effective in patients with higher eosinophil counts (≥300/mm^3). FeNO and blood eosinophil cut-offs were identified based on analysis of the NHLBI Severe Asthma Research Program [16]. Different cut-offs have been investigated (blood eosinophils, 150, 400/mm^3; FeNO, 25, 50 ppb [data not shown]), albeit with no significant differences compared with the thresholds we used.

To date, eosinophils have been considered the main clinical marker of T_H2-type inflammation in respiratory diseases, although their relevance in identifying severity of asthma is still a matter of debate [16,19-21]. The literature reveals a substantial lack of correlation between blood eosinophil count and severity of asthma [16,22,23]. Consistent with our results, this finding seems to be independent of the asthma assessment criterion, including Global Initiative for Asthma parameters, lung function assessment, and PROs.

Blood eosinophilia has been identified as a risk factor for asthma exacerbations, independently of symptom control [20,21]. Our findings did not confirm this correlation. In fact, looking at the variables related to asthma exacerbations, including emergency department admissions, hospital admissions, unscheduled visits, and working days lost, no statistically significant differences could be identified between the high- and low-eosinophil-count subgroups (Table 2). While the rate of admission for asthma exacerbations can be considered more a hallmark of asthma control than of asthma severity, its relationship with blood eosinophil count is also controversial [16,20,21,24,25]. There may be a number of reasons for these divergent findings. Physiologically, eosinophils are characterized by high intra- and interindividual variability [26]. Furthermore, especially in real-life studies, the impact of oral corticosteroids and other drugs influencing blood eosinophil levels cannot be completely ruled out. Our analysis excluded patients taking oral corticosteroids at the time of the baseline blood eosinophilia and clinical assessment in order to increase the homogeneity of the population sample. For the same purpose, we verified previous use of oral corticosteroids, which we found to be homogenously distributed in the high- and low-eosinophil-count subgroups.

The sputum eosinophil count has been reported to be more accurate than the blood eosinophil count as a hallmark of asthma severity [16,23,27,28], and the correlation between the 2 biomarkers seems to be weak [16,26], although reports are controversial [29,30]. In our study, sputum eosinophil count was not assessed, and this could represent a limitation. However, a correlation between blood and sputum eosinophilia has been reported [29,30], and blood eosinophil count was recently found to be a better predictor of response to eosinophil-targeted biological treatments than sputum eosinophil count [19,31]. According to a recent Cochrane review, more evidence is necessary before asthma management can be tailored based on the sputum eosinophil count. Therefore, the approach cannot be currently recommended, unless it is included as part of a multiple-approach evaluation [32]. Furthermore, since investigation of sputum eosinophilia is time-consuming and not widely available, it cannot be considered a simple tool for the evaluation of severe asthmatic patients "at a glance".

FeNO enables a more immediate evaluation, although a number of unrelated factors, including diet and upper airway inflammation, may account for its variability [12]. According to our findings, in contrast with blood eosinophils, a FeNO cut-off of 30 ppb highlighted key differences in the study population, particularly in terms of the hospital admissions rate in the previous year, ACT, AQLQ, and working days lost in the previous year. Therefore, FeNO seemed to be more reliable as a marker of asthma severity and control than eosinophil count, at least in patients with severe allergic asthma. However, the correlation between sputum eosinophil count, blood eosinophil count, and FeNO is not supported by unequivocal evidence [16,33,34]. In addition, the level of agreement between FeNO levels and clinical parameters, including PROs and lung function, differs according to the study [34-37]. Given the better accuracy of FeNO in defining asthma severity and control in our population, we assessed a composite index including both eosinophil count (cut-off, 300 eosinophils/mm^3) and FeNO (cut-off, 30 ppb). The combined score did not improve the accuracy of the individual parameters in determining the clinical severity of the disease. Similarly, while aiming to investigate potential predictors of sputum eosinophils, Hastie et al [16] demonstrated that blood eosinophil count, FeNO, FEV_1 % predicted, and IgE, alone or included in multiple indexes, did not have sufficiently accurate predictive value for exacerbations or application in clinical practice in patients with severe asthma.

As a secondary outcome of our study, we investigated the association between baseline blood eosinophil count and response to omalizumab. The high-eosinophil-count group included more responders than those with <300/

mm^3 at the first follow-up visit, 6 months after initiation of treatment, and at each time-point. Although this trend was not statistically significant, the *P* value for the difference between the subgroups decreased gradually, suggesting that a longer follow-up time frame would have shown a statistically significant difference between the proportion of responders in the 2 subgroups. Nevertheless, the trend was clinically relevant. Furthermore, the proportion of responders in both subgroups increased at each time-point, although in the low-eosinophil-count group, the increase was greater. These findings suggest that within the low-eosinophil-count subgroup, response to treatment may not be time-dependent, and continuing treatment after 6 months does not seem likely to increase the number of responders. The relevance of blood eosinophils in predicting response to biological drugs, particularly T_H2-targeting drugs, has been highlighted by various reports [5-11,38]. As far as omalizumab is concerned, while blood eosinophils are traditionally considered a marker of positive treatment outcome [5,38], a recent large-scale real-life investigation demonstrated that the anti-IgE drug is effective irrespective of baseline eosinophil level [39]. However, as commented on by the authors, the retrospective, real-life design of the study may account for differences with respect to the results of randomized controlled clinical trials, as may the more severe asthma phenotype of patients included in the former. The aforementioned physiological intra- and interindividual variability in eosinophil levels may also explain some findings, as well as the potential effect of oral corticosteroids or other drugs influencing blood eosinophil levels, particularly in the real-life life setting, where strict inclusion criteria are not applied. Katz et al [31] demonstrated that in patients with severe asthma receiving mepolizumab, the reduction in the exacerbation rate was significantly greater in patients with blood eosinophils ≥150/μL than in those with blood eosinophils <150/μL. A recent review including data from the mepolizumab clinical development program confirmed the role of blood eosinophil count as a pharmacodynamic and predictive biomarker of treatment response in patients with severe eosinophilic asthma [19]. Similarly, the 2 randomized clinical trials evaluating reslizumab for poorly controlled asthma demonstrated the crucial role of baseline blood eosinophil level in patient selection [8,9]. Elevated eosinophils also proved to be an essential condition for the efficacy of benralizumab in patients with severe uncontrolled asthma [10,11]. Thus, blood eosinophil count seems to act more as a predictive marker of response to eosinophil-targeting biological treatments than as a hallmark of asthma severity.

Our findings are limited by the retrospective design of the study and the lack of investigation into potential determinants of response and nonresponse other than the blood eosinophil count. However according to the abovementioned studies, the role of eosinophils as predictors of response to treatment does not seem to be significantly affected by other clinical variables.

In conclusion, our findings indicate that blood eosinophil count is not associated with a specific clinical profile in terms of demographic data, total IgE, nasal comorbidities, lung function, and PROs, whilst FeNO, when >30 ppb, is associated with poorer asthma control. We also found the frequency of responders to omalizumab after the first 6-month follow-up to be greater in patients with a higher baseline blood eosinophil count. While not statistically significant, this trend may be relevant from a clinical point of view. Furthermore, continuing treatment after 6 months did not significantly increase the number of responders, particularly in the low-eosinophil-count subgroup. Our findings require confirmation in larger-scale studies. Nevertheless, they should be taken into consideration in the assessment of patients with severe asthma who are candidates for biological treatments.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Ray A, Oriss TB, Wenzel SE. Emerging molecular phenotypes of asthma. Am J Physiol Lung Cell Physiol. 2015;308:L130-L140.
2. Fowler F, Tavernier G, Niven G. High blood eosinophilic counts predict sputum eosinophilia in patients with severe asthma. J Allergy Clin Immunol. 2015;135:822-3.
3. Westerhof GA, Korevaar DA, Amelink M, de Nijs SB, de Groot JC, Wang J, et al. Biomarkers to identify sputum eosinophilia in different adult asthma phenotypes. Eur Resp J. 2015;46;688-96.
4. Arron JR, Choy DF, Scheerens H, Matthews JG. No invasive biomarkers that predict benefit from biological therapies in asthma. Ann Am Thor Soc. 2013;10:S206-13.
5. Hanania NA, Wenzel S, Rosén K, Hsieh HJ, Mosesova S, Choy DF, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med. 2013;187:804-11.
6. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet. 2012;380:651-9.
7. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014;371:1198-207.
8. Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for Inadequately Controlled Asthma With Elevated Blood Eosinophil Levels: A Randomized Phase 3 Study. Chest. 2016;150:789-98.
9. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 Study of Reslizumab in Patients With Poorly Controlled Asthma: Effects Across a Broad Range of Eosinophil Counts. Chest. 2016;150:799-810.
10. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β^2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet. 2016;388:2115-27.
11. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a

randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016;388:2128-41.
12. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am Rev Resp Crit Care Med. 2011;184:602-15.
13. Richards LB, Neerincx AH, van Bragt JJMH, Sterk PJ, Bel EHD, Maitland-van der Zee AH. Biomarkers and asthma management: analysis and potential applications. Curr Opin Allergy Clin Immunol. 2018;18:96-108.
14. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International severe asthma guideline on definition, evaluation and treatment of severe asthma. Eur Resp J. 2014;43;343-73.
15. Caminati M, Senna G, Chieco Bianchi F, Marchi MR, Vianello A, Micheletto C, et al. Omalizumab management beyond clinical trials: the added value of a network model. Pulm Pharmacol Ther. 2014;29:74-9.
16. Hastie AT, Moore WC, Li H, Rector BM, Ortega VE, Pascual RM, et al. Biomarker surrogates do not accurately predict sputum eosinophil and neutrophil percentages in asthmatic subjects. J Allergy Clin Immunol. 2013;132:72-80.
17. Omalizumab Package Leaflet. Available at https://farmaci.agenziafarmaco.gov.it/. Accessed May 20, 2018.
18. Lloyd A, Turk F, Leighton T, Canonica GW. Psychometric evaluation of global evaluation of treatment effectiveness: a tool to assess patients with moderate-to-severe allergic asthma. J Med Econ. 2007;10:285-96.
19. Yancey SW, Keene ON, Albers FC, Ortega H, Bates S, Bleecker ER, et al. Biomarkers for severe eosinophilic asthma. J Allergy Clin Immunol. 2017;140:1509-18.
20. Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. Lancet Respir Med. 2015;3:849-58.
21. Zeiger RS, Schatz M, Li Q, Chen W, Khatry DB, Gossage D, et al. High blood eosinophil count is a risk factor for future asthma exacerbations in adult persistent asthma. J Allergy Clin Immunol Pract. 2014;2:741-50.
22. Amelink M, de Groot JC, de Nijs SB, Lutter R, Zwinderman AH, Sterk PJ, et al. Severe adult-onset asthma: A distinct phenotype. J Allergy Clin Immunol. 2013;132:336-41.
23. Silkoff PE, Laviolette M, Singh D, FitzGerald JM, Kelsen S, Backer V, et al. Asthma characteristics and biomarkers from the Airways Disease Endotyping for Personalized Therapeutics (ADEPT) longitudinal profiling study. Respir Res. 2015;16:142.
24. Malinovschi A, Fonseca JA, Jacinto T, Alving K, Janson C. Exhaled nitric oxide levels and blood eosinophil counts independently associate with wheeze and asthma events in National Health and Nutrition Examination Survey subjects. J Allergy Clin Immunol. 2013;132:821-7.
25. Tran TN, Khatry DB, Ke X, Ward CK, Gossage D. High blood eosinophil count is associated with more frequent asthma attacks in asthma patients. Ann Allergy Asthma Immunol. 2014;113:19-24.
26. Spector SL, Tan RA. Is a single blood eosinophil count a reliable marker for "eosinophilic asthma?" J Asthma. 2012;49:807-10.
27. Schleich FN, Chevremont A, Paulus V, Henket M, Manise M, Seidel L. Importance of concomitant local and systemic eosinophilia in uncontrolled asthma. Eur Respir J. 2014;44:97-108.
28. Inoue H, Ito I, Niimi A, Matsumoto H, Matsuoka H, Jinnai M. CT-assessed large airway involvement and lung function decline in eosinophilic asthma: The association between induced sputum eosinophil differential counts and airway remodeling. J Asthma. 2016;53:914-21.
29. Zhang XY, Simpson JL, Powell H, Yang IA, Upham JW, Reynolds PN, et al. Full blood count parameters for the detection of asthma inflammatory phenotypes. Clin Exp Allergy. 2014;44:1137-45.
30. McGrath KW, Icitovic N, Boushey HA, Lazarus SC, Sutherland ER, Chinchilli VM, et al. A large subgroup of mild-to-moderate asthma is persistently noneosinophilic. Am J Respir Crit Care Med. 2012;185:612-9.
31. Katz LE, Gleich GJ, Hartley BF, Yancey SW, Ortega HG. Blood eosinophil count is a useful biomarker to identify patients with severe eosinophilic asthma. Ann Am Thorac Soc. 2014;11:531-6.
32. Petsky HL, Li A, Chang AB. Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults. Cochrane Database Syst Rev. 2017;8:CD005603.
33. Crespo A, Giner J, Torrejón M, Belda A, Mateus E, Granel C, et al. Clinical and inflammatory features of asthma with dissociation between fractional exhaled nitric oxide and eosinophils in induced sputum. J Asthma. 2016;53:459-64.
34. Calciano L, Portas L, Corsico AG, Olivieri M, Degan P, Ferrari M, et al. Biomarkers related to respiratory symptoms and lung function in adults with asthma. 2018;12:026012.
35. Boulay ME, Boulet LP. Discordance between asthma control clinical, physiological and inflammatory parameters in mild asthma. Respir Med. 2013;107:511-8.
36. Melosini L, Dente FL, Bacci E, Bartoli ML, Cianchetti S, Costa F, et al. Asthma control test (ACT): comparison with clinical, functional, and biological markers of asthma control. J Asthma. 2012;49:317-23.
37. Papakosta D, Latsios D, Manika K, Porpodis K, Kontakioti E, Gioulekas D. Asthma control test is correlated to FEV1 and nitric oxide in Greek asthmatic patients: influence of treatment. J Asthma. 2011;48:901-6.
38. Casale TB, Chipps BE, Rosén K, Trzaskoma B, Haselkorn T, Omachi TA, et al. Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma. Allergy. 2018;73:490-7.
39. Humbert M, Taillé C, Mala L, Le Gros V, Just J, Molimard M, et al. Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study. Eur Respir J. 2018:51(5).

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Marco Caminati

Asthma Center and Allergy Unit, Verona University Hospital
Piazzale Scuro 10
37134 Verona, Italy
E-mail: ma.caminati@gmail.com