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Super-responders to anti-IL-5/anti-IL-5R are characterised by high sputum eosinophil counts at baseline

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ABSTRACT

Several clinical trials have demonstrated that anti-IL-5(R) biologics were able to improve lung function, asthma control and chronic oral corticosteroid exposure and reduce exacerbations among eosinophilic asthmatic patients. However, a certain variability in clinical responses to anti-IL-5(R) biologics was brought to light. Our study aimed at evaluating the role of baseline sputum eosinophils in identifying super-responders to mepolizumab and benralizumab. Our study reinforces the importance to examine sputum eosinophils in patients suffering from severe asthma before starting a biologic as it is associated with the intensity of response to mepolizumab and benralizumab.

SHORT REPORT

Severe asthma is described by the ERS/ATS guidelines as asthma that requires treatment with high-dose ICS plus a second controller with or without systemic corticosteroids to maintain control of the disease or, that remains uncontrolled despite this therapy. Severe eosinophilic asthma represents a clinical inflammatory phenotype associated with greatest risks of exacerbation, hospitalizations, poor asthma control, comorbid nasal polyposis, impaired lung function, and is characterised by a significant number of sputum or blood eosinophils.[1] IL-5 is the key cytokine involved in the maturation, activation and survival of eosinophils and anti–IL-5 biologics were developed to reduce eosinophilic inflammation by inhibiting this type-2 pathway. Among these treatments, mepolizumab is a mAb that targets the ligand IL-5 and benralizumab depletes eosinophils by binding to the IL-5 receptor.[2] Several clinical trials have demonstrated that anti-IL-5(R) biologics were able to improve lung function, asthma control and chronic oral corticosteroid (OCS) exposure and reduce exacerbations among eosinophilic asthmatic patients.[3 4] Some recent studies have however brought to light a certain variability in clinical responses to anti-IL-5(R) biologics.[5–7] Indeed, it appears that some patients are able to reach complete asthma control and some experience sub-optimal response with residual disease manifestations or no response to therapy. Studies reviewing large clinical trials[3 8] highlighted predictors of response to anti-IL-5 treatment. In these clinical trials, higher blood eosinophilia seemed to be a better predictor. However, their definition of response was primarily determined by reduction of exacerbation rate and patients were included based on their blood eosinophil counts. Defining eosinophilic asthma using blood eosinophil concentration could lead to misdiagnosis of patients exhibiting sputum eosinophilia (≥3%) without an increase in blood eosinophil numbers, which represents 25% of asthmatic patients.[1] In fact, Mukherjee *et al*.[9] have shown sub-optimal responses when sputum eosinophilia persists despite normalisation of blood eosinophil numbers with mepolizumab treatment. Here, we aimed at evaluating the role of baseline sputum eosinophils in identifying super-responders to mepolizumab and benralizumab. We conducted a prospective study on 106 patients with severe eosinophilic asthma in whom mepolizumab or benralizumab was started at physician's discretion. Patients were followed in the University Asthma Clinic of Liege between October 2012 and September 2022. Patients fulfilled the reimbursement criteria for mepolizumab and benralizumab in Belgium that require a blood eosinophil count≥300 cells/µL on at least two occasions and a minimum of two exacerbations within the last 12 months. Patients underwent a complete evaluation at baseline and after 24 weeks of treatment. Clinical, functional and inflammatory data were collected at both visits, including sputum cell counts, exacerbation rate, spirometry, chronic OCS use and Asthma Control Questionnaire-7 (ACQ-7). Exacerbations were defined by a course of OCS for at least 3 days for a case of asthma worsening. The study was approved by the Ethics Committee of CHU Liege (Ref. 2009/161), and each patient signed an informed consent. Patients were classified as "super-responders", "partial responders" or "nonresponders" after 24 weeks of treatment. Super-responders met the following cumulative criteria : no exacerbation in the past 24 weeks; a decrease in ACQ-7 score by at least 0.5 or an ACQ-7 score≤1.5; a diminution of sputum eosinophil count (≥ 50%) or a sputum eosinophil count<3%; an improvement of FEV_1 (post-bronchodilation)≥100 mL or FEV_1 (post-bronchodilation)≥80% and a stop of chronic OCS use after 24 weeks of treatment for patients who required daily maintenance with OCS. Nonresponders were patients who didn't achieve a decrease of 50% in OCS dose and didn't reduce their rate of exacerbation (≥ 50%) with mepolizumab or benralizumab therapy after 24 weeks. Finally, partial responders were defined as patients who did not fulfil the criteria of nonresponders and super-responders after 24 weeks of treatment. Comparisons were performed using a Fisher's exact

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Table 1 Demographic, functional and inflammatory characteristics at baseline of patients classified according to their response to mepolizumab and benralizumab.

	MEPOLIZUMAB (n=72) & BENRALIZUMAB (n=34)				
	Super-responders	Partial responders	Nonresponders		
	Median (IQR)/N (%)	*Median (IQR)/N (%)*	*Median (IQR)/N (%)*	*P-value*	N/A (%)
N,%	32 (30)	63 (60)	11 (10)	–	–
Age, years	52 (44, 60)	58 (49, 65)	57 (54, 63)	*0.23*	0
Sex (Male), N (%)	12 (38)	24 (38)	7 (64)	*0.29*	0
BMI, kg/m^2	26.9 (24, 30.4)	26.8 (23.7, 30.2)	27.7 (25, 30.2)	*0.76*	0
Atopy, N (%)	13 (46)	30 (57)	3 (33)	*0.36*	15.1
Bronchiectasis, N (%)	6 (19)	10 (16)	7 (64)*	*< 0.01*	1.9
Nasal polyposis, N (%)	13 (43)	21 (33)	0 (0)*	*0.02*	1.9
Rhinosinusitis, N (%)	7 (27)	16 (32)	3 (33)	*0.89*	19.8
Exacerbations per patient, N	3 (2, 5.2)	2 (2, 3.5)	2 (2, 3.5)	*0.69*	0
ACT score	9.5 (6, 13)	10 (8, 15)	11 (9, 12)	*0.23*	3.8
ACQ score	3.3 (2.5, 4.2)	3.1 (2, 3.6)	3.3 (3, 3.9)	*0.28*	0
AQLQ score	3.3 (2.3, 4)	3.4 (2.6, 4.5)	2.9 (2.7, 4.1)	*0.77*	1.9
PAQ-Y	0 (0, 0)	0 (0, 11)	18 (2.5, 48)*	*< 0.01*	2.8
Smoking status, N (%)				*0.03*	0
Non-smokers	25 (78)	36 (57)	3 (27)		
Ex-smokers	6 (19)	22 (35)	6 (55)		
Smokers	1 (3)	5 (8)	2 (18)		
ICS, N (%)	32 (100)	63 (100)	11 (100)	*1*	0
ICS, mcg	2000 (1,900, 2,625)	2000 (2,000, 3,200)	2000 (2,000, 2,700)	*0.38*	7.5
OCS, N (%)	3 (9)	18 (29)	2 (18)	*0.09*	0
LABA, N (%)	32 (100)	59 (97)	11 (100)	*0.64*	1.9
SABA, N (%)	23 (72)	47 (77)	9 (82)	*0.79*	1.9
LTRA, N (%)	12 (38)	23 (38)	5 (45)	*0.91*	1.9
FE_{NO}, ppb	44 (28.5, 73)	28 (16, 55)	37 (11, 39.5)	*0.05*	0.9
FEV_1 (pre), %	74 (61, 85)	68 (53, 74)*	52 (45, 64)*	*< 0.01*	0.9
FEV_1 (post), %	81 (66, 87)	73 (60, 83)*	61 (48, 71)*	*0.01*	0
FEV_1/FVC (pre),%	71 (61, 79)	69 (59, 76)	63 (59, 70)	*0.27*	1.9
FEV_1/FVC (post),%	71 (63, 82)	72 (63, 78)	69 (64, 74)	*0.43*	2.8
Reversibility, %	9.5 (2, 14.5)	7 (2, 14)	9 (7, 17)	*0.6*	3.8
Blood leukocytes, (x10^3/µL)	8.5 (7.4, 9.8)	8.8 (7.2, 10.3)	8.5 (7, 10.1)	*0.87*	2.8
Blood neutrophils, %	58 (51, 63)	54 (47, 63)	55 (51, 59)	*0.58*	2.8
Blood lymphocytes, %	25 (21, 31)	30 (24, 35)	27 (21, 36)	*0.21*	2.8
Blood monocytes, %	7.6 (6.5, 8.7)	7.4 (6, 9.4)	8.5 (6.4, 9.3)	*0.68*	2.8
Blood eosinophils, %	7 (4.8, 9.9)	5.7 (4, 8.1)	9.4 (3.3, 10.2)	*0.17*	2.8
Blood basophils, %	0.7 (0.5, 1)	0.6 (0.4, 0.9)	0.4 (0.2, 0.9)	*0.19*	2.8
Blood neutrophils, (x10^3/µl)	4.7 (3.8, 6.2)	4.6 (3.6, 6.4)	4.5 (3.7, 6.1)	*0.96*	2.8
Blood lymphocytes, (x10^3/µl)	2.1 (1.7, 2.5)	2.5 (1.9, 3.1)	2.2 (2.1, 2.5)	*0.12*	2.8
Blood monocytes, (x10^3/µl)	0.6 (0.5, 0.8)	0.6 (0.5, 0.8)	0.6 (0.5, 0.9)	*0.78*	2.8
Blood eosinophils, (x10^3/µl)	0.6 (0.4, 0.9)	0.4 (0.3, 0.6)	0.7 (0.3, 0.9)	*0.12*	2.8
Blood basophils, (x10^3/µl)	0.1 (0, 0.1)	0.1 (0, 0.1)	0 (0, 0.1)	*0.26*	2.8
IgE, kU/L	96 (40, 357)	138 (71, 294)	157 (37, 238)	*0.54*	16
Total sputum cell count, (x10^6/g)	2.3 (0.7, 3.7)	1.4 (0.6, 3.7)	1.4 (0.8, 5.6)	*0.76*	0
Squamous cells, %	8 (2, 15)	10 (5, 20)	24 (10, 36)	*0.17*	0
Sputum viability, %	73 (62, 84)	71 (52, 83)	66 (51, 81)	*0.48*	0.9
Sputum macrophages, %	11 (6.7, 23)	11 (7, 17)	8.8 (5.8, 14)	*0.49*	0

Continued

Table 1 Continued

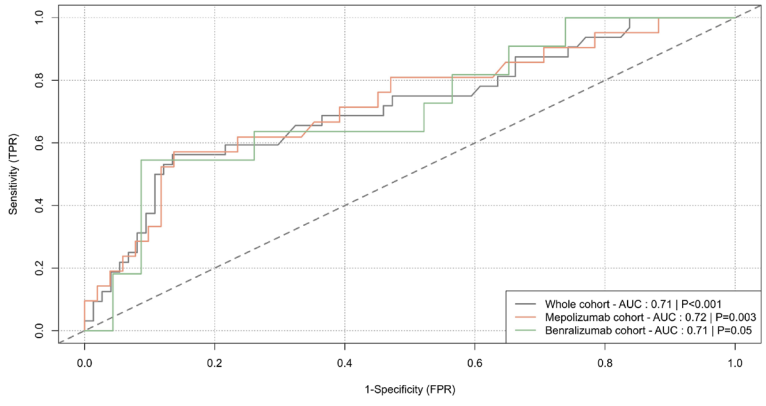
	MEPOLIZUMAB (n=72) & BENRALIZUMAB (n=34)				
	Super-responders	Partial responders	Nonresponders		
	Median (IQR)/N (%)	*Median (IQR)/N (%)*	*Median (IQR)/N (%)*	*P-value*	N/A (%)
Sputum lymphocytes, %	0.6 (0.2, 1.9)	0.2 (0, 0.8)	0.2 (0, 1)	*0.12*	0
Sputum neutrophils, %	37 (22, 54)	64 (48, 78)*	71 (50, 87)*	*< 0.01*	0
Sputum eosinophils, %	41 (11, 52)	8.7 (3.3, 28)*	7 (1.9, 23)*	*< 0.01*	0
Sputum epithelial cells, %	2.8 (1.5, 8.8)	2.2 (0.9, 5)	4.4 (1.6, 8.1)	*0.29*	0

Data were expressed as count and percentage for categorical variables and as median (interquartile range) for quantitative variables.
*p < 0.05, comparison with super-responders determined with post-hoc tests. When multiple comparisons were performed, the statistically significant level was corrected according to Bonferroni principle.
ACQ, asthma control questionnaire; ACT, asthma control test; AQLQ, asthma quality of life questionnaire; BMI,body mass index; FE_{NO}, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid; IgE, immunoglobulin E; LABA, long acting beta agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; PAQ-Y, quantification of cigarette smoking; SABA, short acting beta agonist.

test for categorical variables, an ANOVA test for continuous variables or a Kruskal-Wallis test when parametric assumptions were not met (table 1). Receiver-operating characteristic (ROC) curve was constructed to assess the ability of the sputum eosinophil count (%) to identify super-responders (figure 1). In this cohort, optimal cut-off point was determined by the Youden index method. A p-value<0.05 was considered statistically significant.

The functional, demographic, treatment and inflammatory characteristics at baseline of the severe eosinophilic asthmatic cohort, classified according to their response to benralizumab (n=34) and mepolizumab (n=72) after 24 weeks of treatment are given in table 1. Super-responders represented 30% of the severe eosinophilic asthmatic cohort while partial responders and nonresponders accounted for 60% and 10%, respectively. Super-responders displayed greater baseline sputum eosinophil counts (%) than partial responders and nonresponders (p=<0.01; table 1). The best cut-off point to discriminate super-responders in the whole cohort was 38% of sputum eosinophils (sensitivity, 56%, specificity, 87%, ROC AUC, 0.71, 95% CI, 0.6 to 0.83, p<0.001; figure 1). Specifically, the best cut-off points to discriminate super-responders were 40% of sputum eosinophils for the mepolizumab cohort (sensitivity, 57%, specificity, 86%, ROC AUC, 0.72, 95% CI, 0.59 to 0.86, p=0.003) and 38% of sputum eosinophils (sensitivity, 55%, specificity, 91%, ROC AUC, 0.71, 95% CI, 0.52 to 0.91, p=0.05) for the benralizumab cohort. By contrast, partial responders and nonresponders exhibited a more intense airway neutrophilic inflammation (%) (p<0.01; table 1). Baseline blood eosinophil counts were comparable in all groups, both in absolute value and percentage. Nonresponders were characterised by a greater proportion of bronchiectasis, an absence of nasal polyposis, a more intense smoking history and lower FEV_1 (pre and post,%) values. No difference in baseline FE_{NO} levels was seen between super-responders and nonresponders. Furthermore, change in FE_{NO} over time was not significant and similar between the three groups (data not shown).

Our results highlight that airway type-2 inflammation, defined by high sputum eosinophil counts is better than systemic eosinophilia to identify super-responders to mepolizumab and benralizumab. Other real-life studies have examined super-response to mepolizumab and benralizumab[6 7] and did not identify blood eosinophils as predictors of super-response. Super-response, as per our definition, is a composite outcome that includes but goes beyond the sole exacerbation component. Our data suggest that when taking into account day to day asthma control and lung function improvement, sputum eosinophil count appears to be a better predictor of response to anti-IL-5(R) than blood eosinophils. Importantly, in our study, sputum eosinophils fared much better than FE_{NO} to predict a super-response and the latter does not show any significant change after starting anti-IL-5(R), indicating that the molecular pathway leading to FE_{NO} is clearly independent of IL-5 and eosinophils. In conclusion, our results reinforce the importance to look at airway type-2 inflammatory biomarkers in patients suffering from severe asthma before starting a biologic as it is associated with the intensity of response to mepolizumab and benralizumab.



	Sputum eosinophils (%) cut-off	Specificity (%)	Sensitivity (%)	NPV (%)	PPV (%)
Whole cohort	3	26	91	86	35
	10	51	75	83	40
	20	62	69	82	44
	30	78	59	82	54
	38	87	56	82	64
	40	88	50	80	64
	50	92	28	75	60
	60	93	22	73	58
	70	96	19	73	67
Mepolizumab cohort	3	22	95	92	33
	10	51	81	87	40
	20	61	71	84	43
	30	76	62	83	52
	38	84	57	83	60
	40	86	57	83	63
	50	92	29	76	60
	60	94	24	75	62
	70	96	19	74	67
Benralizumab cohort	3	35	82	80	38
	10	52	64	75	39
	20	65	64	79	47
	30	83	55	79	60
	38	91	55	81	75
	40	91	45	78	71
	50	91	27	72	60
	60	91	18	70	50
	70	96	18	71	67

Figure 1 Roc curves representing the ability of sputum eosinophils (%) to identify super-responders to mepolizumab and benralizumab in combined and separate cohorts associated with cut-off points for sputum eosinophil count (%) for predicting a super-response after logistic regression analysis.

MAIN FINDINGS OF THIS STUDY

Our study reinforces the importance to examine airway type-2 inflammatory biomarkers in patients suffering from severe asthma before starting a biologic as it is associated with the intensity of response to mepolizumab and benralizumab.

Contributors SG and FS designed the study; SG, FS, SG, CM, VP, FG, MH and RL collected the data; SG analysed the data; SG and FS interpreted the data; SG and FS drafted the manuscript; RL revised the manuscript critically for important intellectual content; all authors read and approved the final manuscript.

Competing interests GERDAY Sara, GRAFF Sophie, MOERMANS Catherine, GUISSARD Françoise, PAULUS Virginie and HENKET Monique declare no competing interests. LOUIS Renaud reports grants from GSK, Astrazeneca, Chiesi; royalties from patent AU2016328384, CA2997506, EP 3337393, US2020345266; consulting fees from Astrazeneca; lecture payments from GSK, Chiesi; participation on a data safety monitoring board or advisory board for Astrazeneca ANDHI in practice study and leadership or fiduciary role in other board, society, committee or advocacy group for ERS task force on guidelines on asthma diagnosis, outside the submitted work. SCHLEICH Florence reports grants from GSK, Astrazeneca, Chiesi; consulting fees from GSK, Astrazeneca, Sanofi; lecture payments from GSK, Astrazeneca, Teva, Chiesi and Amgen and support for attending meetings/travel from Chiesi, outside the submitted work.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Ethics Committee of CHU Liege (Ref. 2009/161). Participants gave informed consent to participate in the study before taking part.

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