EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Research letter

Blood eosinophils predict inhaled fluticasone response in bronchiectasis

Stefano Aliberti, Giovanni Sotgiu, Francesco Blasi, Laura Saderi, Tomas Posadas, Miguel Angel Martinez Garcia

Please cite this article as: Aliberti S, Sotgiu G, Blasi F, *et al*. Blood eosinophils predict inhaled fluticasone response in bronchiectasis. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.00453-2020).

Title

Blood eosinophils predict inhaled fluticasone response in bronchiectasis

Authors

Stefano Aliberti MD[1,2], Giovanni Sotgiu MD, PhD[3], Francesco Blasi MD[1,2], Laura Saderi BsC[3], Tomas Posadas MD[4], Miguel Angel Martinez Garcia MD, PhD[4]

Affiliations

[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Respiratory Unit and Cystic Fibrosis Adult Center, Milan, Italy

[2]University of Milan, Department of Pathophysiology and Transplantation, Milan, Italy

[3]Clinical Epidemiology and Medical Statistics Unit, Department of Biomedical Sciences, University of Sassari - Research, Medical Education and Professional Development Unit, AOU Sassari, Sassari, Italy

[4]Pneumology Department. Polytechnic and University La Fe Hospital. Valencia. Spain.

Corresponding author

Stefano Aliberti, MD, Department of Pathophysiology and Transplantation, University of Milan, Respiratory Unit and Cystic Fibrosis Adult Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Francesco Sforza 35, 20122, Milan, Italy. E-mail: stefano.aliberti@unimi.it; tel: +390250320627; cell: +393394171538; fax: +390250320625

Take home message

6-month treatment with inhaled fluticasone propionate significantly improved QoL in bronchiectasis patients who show a blood eosinophil counts ≥3%

Text

The use of inhaled corticosteroids (ICS) in patients with bronchiectasis is matter of debate [1]. International registries report up to 42% of bronchiectasis patients receiving ICS, although several guidelines recommend their prescription only in the presence of specific comorbidities (e.g., Allergic Bronchopulmonary Aspergillosis -ABPA-, asthma, COPD, and inflammatory bowel disease) or of eosinophilic inflammation [2,3]. Assessment of eosinophil counts in sputum is not considered, to date, a standard of care. Blood eosinophils have been shown to be a predictor of ICS response in COPD and asthma [4,5]. The identification of a specific population of bronchiectasis patients who might respond to ICS is key. Response to ICS can be measured in bronchiectasis patients evaluating not only the reduction of exacerbations but also the improvement of their quality of life (QoL). We hypothesized that bronchiectasis patients with a high blood eosinophil count can benefit from ICS in terms of a clinically meaningful improvement of QoL.

An unplanned, *post-hoc* analysis of a randomized, double-blind, controlled, study aimed at evaluating the impact of ICS on QoL in bronchiectasis patients was conducted. Details of the study are reported elsewhere [6]. Adults with clinically and radiologically significant bronchiectasis were enrolled in a single center in Spain. Patients with cystic fibrosis, as well as those with concomitant asthma or ABPA, were excluded. Patients in stable clinical conditions (four weeks out of an exacerbation) were randomized to a 6-month treatment with either 250 μg bid or 500 μg bid of inhaled fluticasone propionate (FP), or no treatment. The primary endpoint was a clinically significant change (≥4 points) in the St. George's Respiratory Questionnaire (SGRQ) total score after 6 months of therapy. Four study groups were considered, based on both the percentage of blood eosinophils at baseline (<3%: low blood eosinophils –LowEos group VS. ≥3%: high blood

eosinophils –HighEos group) and the exposure to fluticasone propionate (no treatment: FP- VS. treatment with fluticasone propionate – FP+). Following the poor scientific evidence on the cut-off value of eosinophils in bronchiectasis studies, the 3% eosinophil threshold has been arbitrarily chosen being the median percentage value in our cohort. Furthermore, the same analysis was conducted using the 150 cells/uL cut off of the absolute eosinophils count (<150 cells/uL: LowEos group VS. ≥ 150 cells/uL: HighEos group). Finally, a sensitivity analysis was conducted excluding patients with a diagnosis of COPD.

Among the 86 patients enrolled in the original study, 42 (48.8%) were in the HighEos and 44 (51.2%) in the LowEos group. In the HighEos group, 13 (31.0%) were not treated, whereas 29 (69.1%) were treated with FP. In the LowEos group, 16 (36.4%) were not treated, whereas 28 (63.6%) were treated with FP. No statistically significant differences were found between the four study groups at baseline in terms of age, gender, treatment with FP, and SGRQ values, see Table 1.a. No statistically significant differences were also found after the exclusion of patients with COPD. Among the entire study population, a statistically significant reduction (≥4 points) of the SGRQ after 6 months of FP was found in the HighEos group between those who were VS. were not treated with FP [15 (51.7%) VS. 0 (0.0%); p-value= 0.0001], (Table 1.a). In the HighEos group, the median (IQR) SGRQ total change was -4.1 (-9.7; 0.4) and 1.6 (0.7; 3.1) in those treated and not treated with FP (p-value: 0.002). In the HighEos group, the proportion of individuals with a modified Medical Research Council (mMRC) scale of 3-4 at 3 months of follow-up was significantly higher in those not treated with FP (23.1% VS. 0.0%; p-value: 0.03), and a higher exacerbation rate was found in those who were not treated vs. those who were treated with FP, although there was no statistically significant difference. No statistically significant differences were found for the mean FEV_1 at 6 months in the HighE group. No statistically significant improvement of QoL was detected in patients with LowE when patients who were administered FP were compared with

those exposed to placebo [10 (37.0%) VS. 1 (6.7%); p-value= 0.06]. No statistically significant differences were found for the exacerbation rate, mean FEV_1 at 6 months, and proportion of MRC 3-4 in the LowE group. The sensitivity analysis based on the exclusion of patients with concomitant COPD confirmed the above-mentioned findings (change of the SGRQ ≥4 points in the HighEos group: 47.4% in patients treated with FP VS. 0.0% in patients treated with placebo; p-value: 0.03). In the HighEos group after exclusion of COPD patients, the median SGRQ total change was -3.7 (-8.5; +5.0) VS. +1 (+0.4; +2.7) in those treated VS. those not treated with FP (p-value= 0.02).

Using the 150 cells/uL cut-off of eosinophils absolute count, a statistically significant reduction (≥4 points) of the SGRQ after 6 months of FP was found in the HighEos group (≥ 150 cells/uL; n= 63 patients) between those who were VS. were not treated with FP [21 (47.7%) VS. 0 (0.0%); p-value= 0.0001]. In the HighEos group, the median (IQR) SGRQ total change was -3.1 (-8.9; 2.8) and 1.6 (0.4; 4.2) in those treated and not treated with FP (p-value: 0.003). Significant differences in terms of reduction (≥4 points) of the SGRQ or the median (IQR) SGRQ total change were not found between those who were VS. those were not treated with FP in the LowEos group (<150 cells/uL; n= 23 patients). The sensitivity analysis based on the exclusion of patients with concomitant COPD confirmed the above-mentioned findings [change of the SGRQ ≥4 points in the HighEos group (≥ 150 cells/uL): 43.3% in patients treated with FP VS. 0.0% in patients treated with placebo; p-value: 0.002]. In the HighEos group (≥ 150 cells/uL) after exclusion of COPD patients, the median SGRQ total change was -1.1 (-8.5; +3.5) VS. +1 (+0.1; +4.2) in those treated VS. those not treated with FP (p-value= 0.03)."

Main findings of this experience include: 1) 6-month treatment with inhaled FP significantly improved QoL in the subgroup of adults with bronchiectasis with an eosinophil counts either ≥3% or ≥ 150 cells/uL; 2) This successful outcome was not found neither in those with an eosinophil counts ≥3% or ≥ 150 cells/uL and not exposed to FP nor in those with an eosinophil counts <3% or

<150 cells/uL exposed or not to FP; 3) The statistically significant improvement of QoL in those patients with an eosinophil count ≥3% or ≥150 cells/uL treated with FP was confirmed also in pure bronchiectasis patients with neither asthma nor COPD; 4) A proportional difference, although not statistically significant, was showed in terms of lower exacerbation rate was showed in those patients with an eosinophil counts ≥3% or ≥ 150 cells/uL and were treated with FP in comparison with those not treated.

Data from local experiences as well as those coming from international registries have informed the scientific and clinical communities about a large proportion of bronchiectasis patients receiving ICS with neither a specific physiopathological rationale nor a strong evidence [2]. Routine use of ICS may cause unwanted side effects in bronchiectasis, including adrenal suppression, an increased risk of hospitalization for respiratory infections, and increased risk of non-tuberculous mycobacteriosis [7-9]. However, a specific T2-high endotype has been hypothesized also in bronchiectasis, with patients presenting an eosinophilic inflammation who might respond to biological drugs [10,11]. Our results should be interpreted as “hypothesis generating”, and we are far from proposing changes in the daily clinical practice. Our preliminary findings support the hypothesis that bronchiectasis patients with neither asthma nor ABPA nor COPD, but with high blood eosinophils, might be the ones who respond to ICS treatment in terms of improvement of quality of life, and encourage further research looking also at a possible effect in reducing exacerbations.

Different limitations can be recognized for the present study. The unplanned secondary analysis of a single-center RCT might be affected by a poor statistical power, hindering the generalizability of the findings. Two different doses of FP were prescribed during the clinical trial, raising the question of a different efficacy of the two regimens. However, owing to the poor sample size, a stratification of the cohort based on the two dosages would have been underpowered. We found

that eosinophils can be a strong predictor of QoL improvement in bronchiectasis, more than in COPD. This finding could be confounded by the open label nature of our study. In fact, although the original study design was a double-blind controlled trial, it is important to acknowledge that the design was unblinded for the purpose of this post-hoc analysis which evaluates ICS VS. placebo. This issue might have impacted patients' evaluation of the quality of life through the SGRQ. Furthermore, although SGRQ is a highly-validated score to measure QoL in patients with chronic respiratory diseases, we now have new, more specific and accurate questionnaires (e.g., QoL-B), not administered at that time, that could be useful for future trials on this topic. Finally, we should acknowledge a low statistical power to detect differences in exacerbation rate due to the low number of exacerbations. Our study was strengthened by a consistency of the results in bronchiectasis patients both with and without COPD, by clinically meaningful improvement of QoL and by a trend also in reducing exacerbations. In conclusion, there are important signals in this secondary analysis that could guide the scientific community in better designing future RCTs on the use of the steroid in light of the value of blood eosinophils.

REFERENCES

1. Kapur N, Petsky HL, Bell S, Kolbe J, Chang AB. Inhaled corticosteroids for bronchiectasis. Cochrane Database Syst Rev. 2018 May 16;5:CD000996.
2. Henkle E, Aksamit TR, Barker AF, Curtis JR, Daley CL, Anne Daniels ML, DiMango A, Eden E, Fennelly K, Griffith DE, Johnson M, Knowles MR, Leitman A, Leitman P, Malanga E, Metersky ML, Noone PG, O'Donnell AE, Olivier KN, Prieto D, Salathe M, Thomashow B, Tino G, Turino G, Wisclenny S, Winthrop KL. Pharmacotherapy for Non-Cystic Fibrosis

Bronchiectasis: Results From an NTM Info & Research Patient Survey and the Bronchiectasis and NTM Research Registry. Chest. 2017 Dec;152(6):1120-1127.

3. Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, Murris M, Cantón R, Torres A, Dimakou K, De Soyza A, Hill AT, Haworth CS, Vendrell M, Ringshausen FC, Subotic D, Wilson R, Vilaró J, Stallberg B, Welte T, Rohde G, Blasi F, Elborn S, Almagro M, Timothy A, Ruddy T, Tonia T, Rigau D, Chalmers JD. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J. 2017 Sep 9;50(3).
4. Harries TH, Rowland V, Corrigan CJ, Marshall IJ, McDonnell L, Prasad V, Schofield P, Armstrong D, White P. Blood eosinophil count, a marker of inhaled corticosteroid effectiveness in preventing COPD exacerbations in post-hoc RCT and observational studies: systematic review and meta-analysis. Respir Res. 2020 Jan 3;21(1):3.
5. Pavord ID, Agusti A. Blood eosinophil count: a biomarker of an important treatable trait in patients with airway disease. Eur Respir J. 2016 May;47(5):1299-303
6. Martínez-García MA, Perpiñá-Tordera M, Román-Sánchez P, Soler-Cataluña JJ. Inhaled steroids improve quality of life in patients with steady-state bronchiectasis. Respir Med. 2006 Sep;100(9):1623-32
7. Holme J, Tomlinson JW, Stockley RA, et al. Adrenal suppression in bronchiectasis and the impact of inhaled corticosteroids. Eur Respir J 2008; 32: 1047–1052.
8. Henkle E, Curtis JR, Chen L, Chan B, Aksamit TR, Daley CL, Griffith DE, Winthrop KL. Comparative risks of chronic inhaled corticosteroids and macrolides for bronchiectasis. Eur Respir J. 2019 Jul 18;54(1).
9. Andréjak C, Nielsen R, Thomsen VØ, Duhaut P, Sørensen HT, Thomsen RW. Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. Thorax. 2013 Mar;68(3):256-62

10. Rademacher J, Konwert S, Fuge J, Dettmer S, Welte T, Ringshausen FC. Anti-IL5 and anti-IL5Rα therapy for clinically significant bronchiectasis with eosinophilic endotype: a case series. Eur Respir J. 2020 Jan 23;55(1).
11. Carpagnano GE, Scioscia G, Lacedonia D, Curradi G, Foschino Barbaro MP. Severe uncontrolled asthma with bronchiectasis: a pilot study of an emerging phenotype that responds to mepolizumab. J Asthma Allergy. 2019 Mar 5;12:83-90.

TABLE

Table 1. Baseline characteristics and outcomes of the four study groups. Table 1.a using the 3% eosinophil cut-off and Table 1.b using the 150 cells/uL cut-off

Table 1.a							
Variable		**LowEos Group (Eos <3%)**		**p-value**	**HighEos Group (Eos ≥3%)**		**p-value**
		FP+	**FP-**		**FP+**	**FP-**	
		n= 28	**n= 16**		**n= 29**	**n= 13**	
Baseline data							
Median (IQR) age, years		73 (68.5-78.0)	69.5 (68-75)	0.35	67 (63-73)	72 (66-75)	0.09
Males, n (%)		20 (71.4)	8 (50.0)	0.16	18 (62.1)	9 (69.2)	0.65
Median (IQR) BMI, kg/m^2		27.3 (25.0-29.6)	26.6 (26.0-29.0)	0.96	27.1 (25.5-29.1)	29.8 (28.3-31.3)	0.06
Etiology, n (%)	**Idiopathic**	15 (53.6)	6 (37.5)	0.38	12 (41.4)	4 (30.8)	0.82
	Post-infective	7 (25.0)	4 (25.0)		9 (31.0)	7 (53.9)	
	Post-tuberculous	5 (17.9)	3 (18.8)		6 (20.7)	2 (15.4)	
	Other	1 (3.6)	3 (18.9)		2 (7.0)		
Purulent sputum, n (%)		10 (35.7)	7 (43.8)	0.60	9 (31.0)	3 (23.1)	0.72

Median (IQR) BORG		3 (2-5)	3 (2.5-4.5)	0.97	3 (2-5)	3 (2-5)	0.92
COPD, n (%)		5 (17.9)	3 (18.8)	1.00	10 (34.5)	4 (30.8)	1.00
Median (IQR) FEV_1 absolute count		1260 (955-1630)	1310 (1120-1830)	0.53	1350 (1116-1670)	1250 (980-1600)	0.39
Median (IQR) FEV_1, %		56 (41.5-77.5)	57.5 (50-72)	0.71	62 (42-70)	60 (51-85)	0.37
Median (IQR) CRP		0.8 (0.2-1.2)	0.5 (0.2-1.0)	0.49	0.7 (0.5-1.1)	0.6 (0.3-1.1)	0.35
Median (IQR) sputum		10 (10-30)	17.5 (5-40)	0.65	20 (10-40)	10 (10-20)	0.43
Gram-positive PMM, n (%)		6 (21.4)	0 (0.0)	0.07	3 (10.3)	1 (7.7)	1.00
mMRC basal, n (%)	0	2 (7.1)	3 (18.8)	0.56	1 (3.5)	1 (7.7)	0.58
	1	6 (21.4)	1 (6.3)		7 (24.1)	5 (38.5)	
	2	15 (53.6)	9 (56.3)		13 (44.8)	5 (38.5)	
	3	4 (14.3)	3 (18.8)		8 (27.6)	2 (15.4)	
	4	1 (3.6)	0 (0.0)				
Median (IQR) exacerbations post-randomization		1 (0-2)	1 (0-1)	0.58	1 (0-1)	1 (1.0-1.5)	0.81
Median (IQR) baseline SGRQ		42.8 (31.6-55.4)	45.8 (36.2-60.6)	0.25	50.8 (33.9-61.5)	41.5 (25.2-51.5)	0.21
Outcome Data							
Variable		**LowEos Group**	**p-value**	**HighEos**	**p-value**	**Variable**	**LowEos Group**

	(Eos <3%)		Group (Eos ≥3%)			(Eos <3%)
Change SGRQ >=4 points, n (%)	10 (37.0)	1 (6.7)	0.06	15 (51.7)	0 (0.0)	0.001
Median (IQR) SGRQ total change*	+0.5 (+5.2; -5.7)	+0.4 (+4.5; -2.0)	0.42	-4.1 (+0.4; -9.7)	+1.6 (+3.1; +0.7)	0.002
Mean (SD) FEV_1 at 6-month, ml	1,524 (369.3)	1,476 (607.0)	0.86	1,429 (470.5)	1,404 (212.0)	0.90
Mean (SD) FEV_1 at 6-month, %	61.4 (19.6)	66.4 (19.6)	0.59	64.8 (19.2)	65.6 (17.1)	0.93
mMRC (3-4) at 3-month, n (%)	5 (17.9)	2 (12.5)	1.0	0 (0.0)	3 (23.1)	0.03
Exacerbations at 6-month, n (%)	12 (57.1)	3 (27.3)	0.15	7 (30.4)	6 (50.0)	0.29

Table 1.b

Outcome data

Variable	LowEos Group (Eos <150 cells/uL)		p-value	HighEos Group (Eos ≥ 150 cells/uL)		p-value
	FP+	**FP-**		**FP+**	**FP-**	
	n= 13	**n= 10**		**n= 44**	**n= 19**	
Change SGRQ >4 points, n (%)	4 (33.3)	1 (11.1)	0.34	21 (47.7)	0 (0.0)	<0.0001
Median (IQR) SGRQ total change*	-2.5 (-5.3; +2.7)	-0.7 (-2.0; +1.6)	0.54	-3.1 (-8.9; +2.8)	+1.6 (0.4; +4.2)	0.003

Mean (SD) FEV1 at 6-month, ml	1,761.3 (614.3)	1,260 (538.7)	0.14	1,371.3 (441.0)	1,610 (393.4)	0.21
Mean (SD) FEV1 at 6-month, %	68.4 (19.6)	58.5 (15.3)	0.33	61.4 (20.3)	72.6 (18.5)	0.21
MRC (3-4) at 3-month, n (%)	3 (23.1)	1 (10.0)	0.60	2 (4.6)	4 (21.1)	0.06
Exacerbations at 6-month, n (%)	7 (70.0)	3 (37.5)	0.34	12 (35.3)	6 (40.0)	0.75

**Difference between the six-month assessment and the baseline value. Footnotes: LowEos: Low-Eosinophil; High-Eos: High-Eosinophil; FP: Fluticasone Propionate; IQR: interquartile range; BMI: body mass index; CRP: C-Reactive Protein; PPM: Potentially Pathogenic microorganism; mMRC: Modified Medical Research Council) Dyspnea Scale; SGRQ: St. George's Respiratory Questionnaire*