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Review Article

Blood eosinophils as biomarkers of therapeutic response to chronic obstructive pulmonary disease: Still work in progress

Salvatore Fuschillo[a], Antonio Molino[b], Cristiana Stellato[c], Andrea Motta[d], Mauro Maniscalco[a,*]

[a] Istituti Clinici Scientifici Maugeri IRCCS, Pulmonary Rehabilitation Division of the Telese Terme Institute, Italy
[b] Respiratory Division, Department of Respiratory Medicine, University of Naples "Federico II", 80131 Naples, Italy
[c] Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, 84081 Baronissi, Salerno, Italy
[d] Institute of Biomolecular Chemistry, National Research Council, 80078 Pozzuoli, Naples, Italy

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ABSTRACT

Disease phenotyping is a key step towards an increasingly personalized approach to chronic obstructive pulmonary disease (COPD), leading to a more precise assessment, treatment and definition of disease outcomes.

The search for biomarkers able to guide the identification of COPD phenotypes are of great importance for both researchers and clinicians. However, while several biomarkers of inflammation [*e.g.*, peripheral blood eosinophils and fractional expired nitric oxide] have been identified and applied in asthma, none has been successfully linked to discrete clinical parameters of COPD such as exacerbations, natural progression, and treatment response or mortality risk.

Recently, several studies have shown that blood eosinophils are a potential biomarker for patient subset stratification in COPD therapy. Here we reviewed the value of blood eosinophils in predicting the response of COPD patients to treatment.

1. Introduction

Chronic obstructive pulmonary disease (COPD) has long been considered a self-inflicted disease, due to the early identification of chronic tobacco smoke habit as key causative agent of the clinical features, and the accelerated decline of lung function characteristic of this disease [1]. Subsequently, accumulating evidence established that a much larger and multifactorial pathogenesis sustains both the onset and progression of COPD, in which complex molecular and cellular alterations result in a common pulmonary presentation featuring cough, dyspnea and wheeze as well as in systemic manifestations [2].

The development of new technology platforms has allowed the acquisition of a huge amount of data about COPD biomarkers. They allow a more in-depth understanding of its pathophysiology but, at the same time, can hinder our knowledge if, when interpreting it, we do not consider the limitations of the data collection techniques, the variations in disease state, activity, impact, and progression [3].

Biomarker research needs to focus on targeted questions in specific patient phenotypes. Disease phenotyping is a key step towards an increasingly personalized approach to COPD, leading to more precise assessment, treatment and definition of disease outcomes. Indeed, a number of COPD phenotypes differing in natural history, degree of severity, exacerbation rates and response to specific treatments have been described [4,5]. Interestingly, a recent study applying clustering to different COPD cohorts indicated that rather than discrete phenotypes, the heterogeneity of COPD reflects continuous disease traits concomitantly expressed, in variable degrees, within each patient [6]. Research efforts have therefore focused on unraveling the pathobiological pathways (endotypes) underlying phenotypes in order to identify "treatable traits" of this so complex disease, defined as phenotypic or endotypic characteristics that can be successfully targeted with treatment.

Endotypic biomarkers able to guide the identification of disease phenotypes are of great importance for both researchers and clinicians: a biomarker should be specific of a phenotype, correlate with disease severity and/or disease control, help physicians in treatment titration in order to maximize its positive effects while minimizing the negative ones [7]. An ideal biomarker should be safe, accurate, reproducible, inexpensive and readily available. While several biomarkers of inflammation (peripheral blood and induced sputum eosinophils, fractional expired nitric oxide (FeNO) have been identified and applied for asthma [8,9], so far none has been successfully linked to discrete clinical COPD parameters such as exacerbations, natural progression and treatment response or mortality risk [10,11].

* Corresponding author at: Istituti Clinici Scientifici Maugeri IRCCS, Via Maugeri 4, 27100 Pavia, Italy.
E-mail address: mauro.maniscalco@icsmaugeri.it (M. Maniscalco).

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2. Eosinophilic inflammation in COPD: is there a role as a phenotype biomarker?

Eosinophilic inflammation represents the hallmark of airway inflammation in a subset of asthma, mostly allergic in origin, and is orchestrated by a T2-mediated immune response. Conversely, a Th1/Th17-mediated immune response with airway neutrophilic inflammation, often in relation with bacterial colonization, is largely observed in the airways of COPD patients [12,13]. However, just as a subset of patients with asthma can be characterized by a neutrophilic inflammation, eosinophilia in the blood or in the sputum of COPD patients is well documented [14]. Airway eosinophilic inflammation is found in about 10–40% of stable COPD patients [15,16], and an eosinophilic-predominant phenotype has been found in 28% of exacerbations [17] with the degree of eosinophilia found to be higher than in stable disease [15]. Along the same lines, eosinophilic inflammation is deemed to be a predictor for future COPD exacerbations [18]. Moreover, the presence of sputum eosinophils ≥3% in asthma and COPD [19,20] and the T2 gene signature [21] have been found to be a good predictor of response to corticosteroid treatment. In particular, sputum eosinophil counts of ≥3% has been proposed as cut-off value for the definition of eosinophilic COPD [17]. However, eosinophilic COPD patients cannot easily be distinguished based on clinical characteristics alone [22], and induced sputum is an expensive, technically demanding, time consuming and not widely available technique.

Recently, new therapeutic options targeting eosinophilic or related pathways have been introduced, and the availability of biomarkers able to identify COPD patients, which would benefit of such new therapies, is an unmet need of utmost clinical importance. Blood eosinophil count has been proposed as a surrogate of sputum eosinophils' biomarker for eosinophilic COPD phenotypes [23] because it is readily accessible in clinical practice and is applicable in all patients. Furthermore, there are data suggesting a moderate correlation between blood eosinophil and sputum eosinophil count ($r = 0.6$; $p < .0001$) [24] ($r = 0.59$; $p < .001$) [23]. Accordingly, clinical evidence appears to indicate usefulness of peripheral blood eosinophilia as a biomarker, mostly for evaluation of the risk and/or occurrence of exacerbation and as predictor of therapeutic response - to corticosteroid use first and then also to select patients for therapy with specific biologicals. However, there is still a grey area in several parameters, which hampers sensitivity and specificity of peripheral blood eosinophilia before they can become a valid biomarker in COPD therapeutic response.

3. Exacerbations risk in COPD: are eosinophils the guiding light?

Increased blood eosinophil count in COPD has been well linked to clinical manifestations. Patients with elevated blood eosinophil count during stable disease (≥ 450 cells/μl) reportedly display a 13% higher exacerbation rate during the following year than patients with lower counts ($p = .03$) [25]. A 2% cut-off point for blood eosinophils – within normal range as it is approximately equivalent to 150 cells/μl in absolute count [26] - has been used as the threshold in the majority of studies for predicting eosinophil-associated airway inflammation and eosinophil-associated exacerbations [27] based on high sensitivity in predicting sputum eosinophilia [28]. In a community population study with an over 30-year follow-up, Hospers et al. [29] showed that blood eosinophil count ≥275 cells/μl was associated with a 40% increased mortality, and a 4.8-fold increased risk of death from COPD in patients with a history of exacerbations [30]. In another study, a baseline blood eosinophil count > 340 cells/μl was associated with a 1.76-fold increased risk of severe exacerbations and a 1.15-fold increased risk of moderate exacerbations [31]. However, in the ECLIPSE study, in which approximately 90% of patients were receiving ICS at baseline, no difference in exacerbation rates was observed (either prior to study entry or over the 3-year observational period) for patients with ≥2% *vs.* < 2% blood eosinophils [32]. Similar negative results for this readout were also reported in a retrospective study evaluating its association with severe exacerbations requiring hospitalizations [28].

4. Eosinophilia to identify inhaled corticosteroid (ICS)–responsive COPD exacerbations

Inhaled and oral corticosteroids have long been considered the drugs of choice to decrease eosinophilia in peripheral blood and tissues [33] [34], an important anti-inflammatory step in asthma therapy. The effects could also interfere with the COPD course, possibly reducing exacerbations and the decline of the lung function [35]. The re-analyses of large trials involving ICS-containing treatments in COPD have shown a relationship between the blood eosinophil count and the risk of exacerbations. More importantly, they revealed that the reduced risk of exacerbations brought about by ICS, or adding ICS to a LABA-only regimen [36,37], or with the use of ICS/LABA *vs.* LAMA, is absent or minimal in patients with a blood eosinophil count ≤2%, increasing progressively above this level [38]. Furthermore, Bafadhel and colleagues [39] showed that the preventive effect of budesonide was relevant above 100 eosinophils/μl, while the effect size increased gradually from a 25% relative reduction in the 100–190 cells/μl range, to 26–50% in the 200–340 cells/μl range, and 51–60% in the 350–630 cells/μl range.

The TRINITY study compared treatment with extrafine beclomethasone dipropionate, formoterol fumarate and glycopyrronium bromide (BDP/FF/GB; fixed triple) with tiotropium, and BDP/FF plus tiotropium (open triple) over a 1-year period [18]. It showed that in patients receiving BDP/FF/GB *vs.* tiotropium, in the lower eosinophil group (< 2%) exacerbations were not significantly reduced by 7–8%, whereas in the ≥2% group exacerbations were significantly reduced by 30% [40].

In the INSPIRE study (fluticasone propionate/salmeterol *vs.* tiotropium), in patients with blood eosinophils ≥2% LABA/ICS treatment was associated with significantly reduced exacerbation rates compared with LAMA ($p = .006$) [38]. Similarly, in the TRISTAN study (fluticasone propionate /salmeterol *vs.* salmeterol, fluticasone propionate, or placebo) patients with eosinophils ≥2% treated with LABA/ICS had significantly reduced exacerbation rates *vs.* placebo-treated patients ($p = .001$) but not *vs.* LABA or LAMA [41]. Significant differences *vs.* placebo were also observed for LABA alone and ICS alone ($p = .02$ and $p = .005$, respectively). Similar to the findings of the TRINITY study, no significant differences were observed in either study for patients with < 2% eosinophils [38]. A post-hoc analysis of a small trial of 248 patients with COPD also reproduced this response pattern, showing that exacerbation rate was significantly decreased in patients with blood eosinophil levels ≥3% who were treated with high- (1000 μg/day) or low-dose (500 μg/day) fluticasone with respect to patients with blood eosinophils < 3% [42]. In another post-hoc analysis of the FORWARD study, Siddiqui et al. [37] reported that patients with eosinophils ≥279.8 cells/μl gained a greater benefit from beclometasone/formoterol *vs.* formoterol alone if compared with patients with lower blood eosinophils. Pooled analysis of the LANTERN and ILLUMINATE trials also demonstrated that fluticasone/salmeterol was more effective than indacaterol/glycopyrronium at reducing exacerbation risk in COPD patients with blood eosinophil counts ≥300 cells/μl [43].

Finally, in a large meta-analysis including 12,496 patients with moderate-to-very severe COPD, exacerbations were reduced of 17% in patients undergoing ICS therapy with blood eosinophils ≥2% as compared to the non-ICS/ICS withdrawal/placebo group. No significant difference in the subgroup with eosinophil count < 2% was observed [44].

Along the same lines, post-hoc analyses of several studies on COPD patients indicated that upon ICS treatment the risk of exacerbation after ICS withdrawal increases according to blood eosinophil count. WISDOM was a 52-week phase-4 study comparing exacerbation risk in patients who continued triple therapy with a LAMA + LABA + ICS with those who had ICS withdrawn after 6 weeks [45]. In a post-hoc

Table 1
Eosinophil thresholds to identify inhaled corticosteroid – responsive COPD exacerbations in recent COPD clinical trials.

Author (References)	Subjects	Study treatment	Eosinophil thresholds	Clinical findings
Bafadhel [39]	4528	BDP/FOR *vs.* FOR	100–190 cells/μl	↓25% risk exacerbation
				↓26–50% risk exacerbation
			200–340 cells/μl	↓51–60% risk exacerbation
			350–630 cells/μl	
Vestbo [40]	2691	BDP/FF/GLY *vs.* tiotropium and BDP/FF + tiotropium	< 2%	↓7–8% risk exacerbation (not statistically significant)
			≥2%	↓30% risk reduction
Pavord [38]	1323	FP/SAL *vs.* tiotropium	≥2%	↓exacerbation rate (p = .006)
			< 2%	No significant difference ($P \leq .186$)
Calverley [41]	1465	FP/SAL *vs.* SAL, FP or placebo	≥2%	↓25% exacerbation rate in FP/SAL *vs* placebo (p = .001)
			< 2%	↓20% exacerbation rate in SAL *vs* placebo (p = .0022)
				↓19% exacerbation rate in FP *vs* placebo (p = .0033)
				No difference observed
Cheng [42]	248	FP/SAL 1000/100 μg/day (HD)	≥3% (HE)	Acute exacerbation HE/HD 13.5%
		FP/SAL 500/100 μg/day (MD)	< 3% (LE)	Acute exacerbation LE/HD 22.6%
				Acute exacerbation HE/MD 14.7%
				Acute exacerbation LE/MD 28.7%
Siddiqui [37]	1199	BDF/FOR *vs.* FOR	< 110.4/μl	↓22%exacerbation rate (p = .113)
			100.4 < 181.6 μl	↓23%exacerbation rate (p = .105)
			181.6 < 279.8 μl	↓28%exacerbation rate (p = .041)
			≥ 279.8 μl	↓46%exacerbation rate ($p \leq .001$)
Vogelmeier [43]	1263	IND/GLY (QVA149) *vs.* SAL/ Fluticasone (SFC)	< 150/mm^3	QVA149 ↓45% in the risk of exacerbations compared to SFC
			150–300/ mm^3	QVA149 ↓43% in the risk of exacerbations compared to SFC
			> 300/mm^3	Risk of exacerbations lower with SFC.
Cheng [44]	12,496	ICS	≥2%	17% reduction in exacerbation of moderate/severe COPD in patients with undergoing ICS therapy compared to the non-ICS/ICS withdrawal/ placebo group.
			< 2%	There was no significant difference in this subgroup (p < .181)
Watz [46]	2296	FP/SAL/tiotropium *vs.* continued or withdrawal ICS	< 2%	Exacerbation rate higher in the ICS-withdrawal group *vs* the ICS-continuation group in patients with eosinophil counts of 2% or greater (rate ratio 1·22 [95% CI 1·02–1·48]), 4% or greater (1·63 [1·19–2·24]), and 5% or greater (1·82 [1·20–2·76]).
			≥2%	
			< 4%	
			≥4%	
Wedzicha [47]	3362	IND/GLY *vs.* SFC	< 2%	indacaterol/glycopyrronium *vs.* SAL/fluticasone on the rate of COPD exacerbations was independent of the baseline blood eosinophil count.
			≥2%	
Anzueto [49]	3362	IND/GLY *vs.* SFC	≥300 cells/μl and very severe COPD	IND/GLY significantly reduced the risk of CID *vs.* SFC in all subgroups
				↓risk of CID not statistically significant

Abbreviations: BDP = budesonide dipropionate, FOR = formoterol, FF = formoterol furoate, FP = fluticasone propuionate, SAL = salbutamol, IND = indacaterol, GLY = glycopirronium, ICS = inhaled corticosteroids, CI = confidence Interval, HE = high eosinophils, LE = Low eosinophils.

analysis of the WISDOM data, which compared the rate of exacerbations in relation to blood eosinophil subgroup of increasing cut-off levels after complete ICS withdrawal, Watz et al. [46] reported that continuation of ICS was superior to withdrawal in severe COPD patients with blood eosinophil counts ≥300 cells/μl and a history of frequent exacerbations. On the contrary, in those with < 4% or < 300 cells/μl no consistent effect was observed.

A recent retrospective study focused on the role of circulating eosinophils in predicting exacerbations and response to ICS therapy specifically in COPD patients with severe exacerbations requiring hospitalizations [28]. Differently from other post-hoc analyses, this study found that ICS therapy in addition to dual bronchodilators was not associated with reduction of exacerbation risk at any eosinophil cut-off value, considered both in clinically stable patients and after the first exacerbation (Table 1).

5. Eosinophilia to identify differential treatment effects

Several post-hoc analyses based on studies comparing treatment regimens indicated that rather than guiding therapy choices between LABA/LAMA and LABA/ICS, eosinophilia identifies patients who would benefit from addition of ICS to bronchodilator therapy. The FLAME study is a prospective study that examined differential treatment effects in COPD patients stratified by baseline eosinophils (< 2% *vs.* ≥ 2%) [47]. Over 52 weeks, it compared a LABA/LAMA with a LABA/ICS (indacaterol/glycopyronnium and salmeterol/fluticasone propionate, respectively) in patients with moderate-to-severe COPD and a history of ≥1 exacerbation in the previous year. LABA/LAMA significantly reduced exacerbations *vs.* LABA/ICS by 11% in the overall population (p = .003: primary endpoint), but also irrespective of eosinophil counts (p = .004 and p = .01 for patients in the < 2% and ≥ 2% eosinophil subgroups, respectively) [47]. In a re-analysis of the FLAME data using additional eosinophil cut offs (< 3%, < 5%, < 150 cells/μl, < 300 cells/μl and ≥ 300 cells/μl), similar findings were reported, but a close analysis of data showed a diminishing benefit of LABA/LAMA *vs.* LABA/ICS in patients with a higher baseline blood eosinophil count [48].

Anzueto et al. [49] in a post-hoc analysis of the FLAME study reported that LABA/LAMA, compared to LABA/ICS, significantly reduced the risk of clinically important deterioration in all subgroups except for patients with baseline eosinophil ≥300 cells/μl and for those with very severe COPD. This reinforced the evidence for a role for eosinophils in identifying patients who could benefit from additional ICS to their bronchodilator therapy. Similarly, using data from two large randomized trials evaluating the addition of 50 μg, 100 μg, or 200 μg inhaled fluticasone furoate to once daily vilanterol (25 μg) in patients with moderate-to-severe COPD and with one or more exacerbation in the previous year, Pascoe et al. reported that across all doses of ICS, fluticasone furoate and vilanterol reduced exacerbations by 29% compared with vilanterol alone (p < 0·0001) in patients with eosinophil counts of ≥2%, and by 10% (p = .2827) in patients with eosinophil counts ≤2% [36]. Fluticasone furoate and vilanterol as compared to vilanterol alone obtained an exacerbations reduction of 24% in patients with baseline eosinophil counts of ≥2– < 4%, of 32% in those with eosinophil counts between 4 and 6%, and of 42% in those with eosinophil counts of ≥6%. A further important observation was that in patients

treated with vilanterol alone, exacerbation rates increased progressively with increasing eosinophil count percentage category.

A recent review by Agustì et al. [50] about the positioning of ICS in the treatment of COPD, suggested that ICS addition to long-acting bronchodilators can most likely benefit patients with a history of multiple or severe exacerbations, and those with blood eosinophils > 300 cells/μl, which has been suggested as a practical cut-off value.

Based on data provided by the recent large randomized controlled trials, the GOLD Science Committee report 2019 introduced blood eosinophil counts in the algorithm of treatment recommendations in COPD patients that exacerbate despite appropriate bronchodilator treatment, therefore supporting the clinical decisions regarding the introduction of ICS in this subset of COPD patients [51].

6. Eosinophils for biological therapy in COPD

Several biologicals are in preclinical or early-stage clinical development for COPD [52], but so far they have not reached approval. In particular, clinical trials with anti-IL-5 and anti-IL-5Rα antibodies in eosinophilic COPD showed either a smaller or no reduction in exacerbation rates, respectively, when compared with severe eosinophilic asthma [53]. This underscores how the presence and pathogenetic role of eosinophils in COPD may be driven by a different mechanism with respect to severe asthma, indicating the need of a better understanding of the pathophysiological role of eosinophilic inflammation in COPD in order to select patients on endotypic basis. Among the biologicals so far evaluated in eosinophylic COPD, Mepolizumab (an anti-IL-5 antibody that affects proliferation, differentiation and migration of eosinophils) showed no significant differences in the annual rate of moderate or severe exacerbations. However, in subjects with higher blood eosinophil counts, a low dose of mepolizumab was associated with a lower annual rate of moderate or severe exacerbations.

Two 1-year phase-3 studies on the efficacy of mepolizumab on exacerbation prevention in eosinophilic COPD patients were recently reported. In one (METREX), the 100-mg mepolizumab dose induced a significant reduction of moderate/severe COPD exacerbations *vs.* placebo in a subgroup of COPD patients with an eosinophilic phenotype (eosinophil count ≥150 cells/μl at screening or ≥ 300 cells/μl at any point in the previous year), but not in the overall population. The second study (METREO), which was conducted in COPD patients, showed no difference *vs.* placebo for the 100-mg and 300-mg doses. In a pre-specified meta-analysis, the authors were able to show that the greater effect on exacerbation prevention was observed in patients with higher blood eosinophil counts (≥ 300 cells/μl at screening) [54].

7. Gaps in knowledge

The data reported above indicate that peripheral blood eosinophils can have a role as a surrogate marker to identify a subset of COPD patients who are at risk of exacerbation. They may benefit from addition of ICS during exacerbations or to bronchodilator therapy, although, as pointed out, there are analyses that do not confirm these associations. At any rate, the positive effects of ICS need to be offset against the risk of adverse events. This is particularly relevant given that the ICS use in COPD patients has been linked to increased pneumonia incidence, as well as to other comorbidities, especially with its long-term use [55].

Importantly, the lack of clinical response to eosinophil-targeting biological treatments so far points at yet to be identified roles for eosinophils in COPD. It would be of particular relevance in guiding appropriate patient stratification for a targeted strategy. Therefore, there are still several gaps in our knowledge that must be filled and addressed in preclinical and clinical studies before peripheral blood eosinophils can be adopted in clinical practice as a biomarker to guide choice of treatment.

In particular:

1. Blood eosinophil count provides no information on the site of inflammation, and therefore it is likely to lack specificity as a biomarker of eosinophilic airway inflammation [56].
2. Measurements of blood eosinophils need to be stable and reproducible when considering it as a biomarker. The stability and therefore the reproducibility of blood eosinophil measurements has been questioned, as fluctuations occur over time [32,57]. Eosinophil counts can fluctuate because their half-life in blood is short and they show a diurnal variation, with a peak in the evening [58].

In the ECLIPSE cohort, using 2% as blood eosinophil cut-off value, over a period of 3 years [32] blood eosinophils were persistently elevated in 37% of subjects, intermittently elevated in 49%, while the remainder of subjects were noneosinophilic [32]. In an 8-year follow-up with COPD patients and matched controls, the percentage of subjects with persistent blood eosinophil count ≥340 cell/μl was 80% at 6 months and 30% at 4 years, declining to 18% at 8 years. In addition, eosinophil stability was significantly lower in COPD patients *vs.* controls, and in patients with higher eosinophil count ≥340 *vs.* those with lower values [59].

3. Blood eosinophil count is a continuous variable with no sharp cut-off point. In most studies, a 2% cut-off value has been adopted, which has not been confirmed as an optimal value. The optimal cut-off value to predict exacerbation risk can be different from that to predict response to treatment and different cut-offs may be needed for different endpoints [60]. A 2% blood eosinophil value may be too low to accurately identify the subset of COPD patients that could most likely benefit from ICS treatment [44]. However, percentage of blood eosinophils is relative to patients' white blood cell count, and therefore, absolute blood eosinophil count may be within the normal range, or even lower than 2% if white blood cell count is low [48].
4. Exercise and smoking may increase the blood eosinophil count, but their specific impact on COPD is unknown [61].

8. Conclusions

A recent consensus from the GOLD scientific committee on current controversies in COPD underscores the large unmet need for blood biomarkers for diagnosis, risk stratification and treatment response for COPD [62]. In particular, it lists the use of peripheral eosinophils as biomarker essentially as a work in progress, citing "*evolving evidence that blood eosinophil levels may be associated with important outcomes in patients with COPD*", advocating more prospective and controlled trials to validate its practical value as treatment biomarker.

Preclinical research, also drawing from the lack of therapeutic response with eosinophil-targeting biologicals, is necessary to better characterize the unique role of eosinophils in COPD pathogenesis. Further clinical work is also needed to identify the optimal blood eosinophil cut-off point for phenotyping patients with COPD. Considering the variations over time, this is a crucial point to identify the different cut-off values that may be required depending on the context of use, to address the question of whether blood eosinophils are helpful to guide initiation of ICS therapy and/or monitoring its course.

GOLD 2019 pharmacological treatment recommendations of COPD indicate blood eosinophils as a useful biomarker to support clinical decisions to add ICS to appropriate long acting bronchodilators. A cut-off value of blood eosinophils > 300 cells/μl seems to identify the top of the continuous relationship between eosinophils and ICS. Such a value is now recommended to identify patients with the greatest likelihood treatment benefit with ICS.

Declaration of Competing Interest

None.

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