Clinical and inflammatory markers in asthma and COPD phenotyping

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Chapter 6

EXTERNAL VALIDATION OF SERUM PERIOSTIN, FENO AND BLOOD EOSINOPHILS AS SURROGATES FOR SPUTUM EOSINOPHILS IN ASTHMA

Submitted

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Abstract

**Background:** Monitoring sputum eosinophils in asthma predicts exacerbations and improves asthma management. Thus far, blood eosinophils and fraction of exhaled nitric oxide show contradictory results in predicting eosinophilic airway inflammation. More recently, serum periostin was proposed as a novel biomarker for sputum eosinophils.

**Objectives:** Quantifying the mutual relationships of blood eosinophils, FeNO and serum periostin with sputum eosinophils by external validation in two independent cohorts across various severities of asthma.

**Methods:** 110 patients with mild to moderate asthma (external validation cohort) and 37 patients with moderate to severe asthma (replication cohort) were cross-sectionally evaluated. Sputum was induced for the assessment of eosinophils. In parallel, blood eosinophil counts, serum periostin concentrations and FeNO were assessed. The diagnostic accuracy of these markers to identify eosinophilic asthma (sputum eosinophils ≥3%) was calculated using receiver operating characteristics (ROC AUC).

**Results:** In the external validation cohort, ROC AUC for blood eosinophils was 89% (p<0.001) and for FeNO level 78% (p<0.001) to detect sputum eosinophilia ≥ 3%. Serum periostin was not able to distinguish eosinophilic from non-eosinophilic airway inflammation (ROC AUC= 55%, p=0.44). When combining these three variables no improvement was seen. The diagnostic value of blood eosinophils was confirmed in the replication cohort (ROC AUC 85%; p<0.001).

**Conclusion:** In patients with mild to moderate asthma as well as patients with more severe asthma blood eosinophils have the highest accuracy to identify sputum eosinophilia in asthma. This can facilitate individualised treatment and asthma management.
Introduction

Asthma is a heterogeneous condition including several clinical phenotypes that differ in severity, natural history, and responses to therapy (1). There is recent evidence from prospective clinical studies that inflammatory (sub)phenotyping of patients can help to optimize therapy and disease outcome (2). This indicates that biomarkers of inflammation should be considered in the monitoring of asthma in clinical practice.

Sputum eosinophilia appears to be a key marker in predicting asthma outcome (3). Whereas eosinophilic asthma responds well to anti-inflammatory treatment with steroids, non-eosinophilic asthma shows little or no response (4). In addition, studies in which corticosteroids were withdrawn have consistently shown that a raised sputum eosinophil count is predictive of inducing an exacerbation (5;6). The definitive evidence that monitoring sputum eosinophils improves outcome has come from randomized trials showing that normalizing sputum eosinophil counts can lead to 60% reduction in asthma exacerbations (2;7;8).

Sputum induction by hypertonic saline is generally considered a reliable non-invasive method to assess and monitor eosinophilia (9). However, the application of sputum analysis is hindered by the requirement of lab facilities and the duration of the analyses. Furthermore, in patients with severe and uncontrolled asthma, induction of sputum can be problematic, because of hypertonic saline-induced airway narrowing and/or failure to produce an adequate sputum samples in about a quarter of the patients (10).

Therefore, there is a need for adequate surrogate markers of eosinophilic inflammation in asthma. The measurement of fractional exhaled nitric oxide (FeNO) has been considered a surrogate marker for eosinophilic airway inflammation. However, the correlation between FeNO and sputum eosinophils appears to be only modest (11), particularly in patients with steroid-dependent asthma (12). This is in line with a Cochrane meta-analysis demonstrating insufficient benefit of monitoring steroid therapy by FeNO (2). Alternatively, blood eosinophil counts exhibit moderate to good correlation with sputum eosinophils in asthma (13), being associated with disease severity (14) and asthma phenotypes (15). Blood eosinophils may therefore predict and direct anti-inflammatory therapy, for which there is preliminary evidence in asthma (16) and chronic obstructive pulmonary disease (17). Nevertheless, a very recent study demonstrated poor correlations of FeNO and blood eosinophils with sputum eosinophils, both separately and combined (18), thereby raising controversy. Finally, periostin was proposed as a systemic biomarker of eosinophilic airway inflammation in asthma, by showing a significant correlation with sputum eosinophils (19) and prediction of steroid responsiveness in asthma (20).

Based on international STARD-guidelines (21) it is mandatory to perform external validation when assessing diagnostic or phenotypic accuracy of disease markers. This
has not been done for sputum eosinophils with the triad FeNO, blood eosinophils and serum periostin. Therefore, we aimed to quantify the mutual relationships of FeNO, blood eosinophils and serum periostin with sputum eosinophils in an external validation cohort of patients with mild to moderate asthma, and to replicate findings in a population with more severe asthma.

Methods

Subjects

For the external validation-cohort we recruited 200 patients with mild to moderate asthma in the outpatient clinic of the Academic Medical Center (AMC) in Amsterdam and two non-academic pulmonary 2nd line referral outpatient clinics. For the replication-cohort we recruited 40 patients with moderate to severe asthma in the outpatient clinic of the AMC. For both cohorts, the diagnosis of asthma was defined by a physician’s diagnosis of asthma with reversibility in FEV₁ ≥ 12% of the predicted value and/or airway hyperresponsiveness (PC<sub>20</sub> methacholine < 8mg/ml).

In the validation-cohort smokers or ex-smokers with a smoking history > 10 packyears were excluded if they did not show an improvement in FEV₁ of at least 12% after inhalation of 400µg salbutamol with a normal diffusion capacity at the time of inclusion. In the replication-cohort all smokers or ex-smokers with a smoking history > 10 packyears were excluded. At the time of the study visit, all patients had had no symptoms of respiratory infection for at least 4 weeks.

Both studies were approved by the Hospital Medical Ethics Committee and all patients gave their written informed consent. The validation-cohort was registered in the Netherlands trial register (www.trialregister.nl) under NTR1846, the replication-cohort under NTR2364.

Design

The studies had cross-sectional designs and included one hospital visit for all measurements. During this visit inclusion and exclusion criteria were examined, lung function was performed, sputum was induced by hypertonic saline, FeNO was measured and blood was collected.

Inflammatory status in the external validation-cohort was measured by the assessment of blood eosinophils, FeNO and serum periostin. In the replication cohort blood eosinophils and serum periostin were measured in order to replicate findings in a population with more severe asthma.
Measurements

Lung function and allergy testing
Lung function was performed according to ERS recommendations (22). Atopic status was assessed by total and specific IgE to a panel of common aeroallergens.

Markers of inflammation
Sputum was induced by inhalation of hypertonic saline 3 times at intervals of 5 minutes, according to the ERS recommendations (23). Prior to sputum induction, patients inhaled 400µg salbutamol. For the validation-cohort the volume of the whole sputum sample was assessed and an equal volume of dithiotreitol (10mM DTT in 135mM Tris buffer, pH 8.0) was added. For the replication-cohort selected plugs were processed with 0.1% DTT. Next, cell counts were performed and cytospins were made. Differential cell counts were expressed as the percentage of non-squamous cells, based on 500 non-squamous cells. Those with significant squamous contamination (>80%) were excluded from analysis. According to previous studies (7) we used a sputum eosinophil count of 3% as the threshold for determining eosinophilic or non-eosinophilic airway inflammation.

Peripheral blood eosinophil counts were obtained from standard complete blood counts and FeNO was measured using an online device at a constant flow (Niox Mino; Aerocrine AB, Solna, Sweden) (24). Serum was obtained by centrifugation of blood that coagulated for 30 minutes at room temperature, after which serum periostin levels were measured in an ELISA with the DuoSet Human Periostin/OSF-2 (R&D Systems). Our in-house ELISA for periostin was validated for measurement of periostin in serum by serial dilutions (10x, 20x, 40x and 80x diluted; ± 15.5% variation) and spike recovery (77.75% ± 11.69%; (mean ± SD)). The intra- and inter-assay were ≤12.3% (9.08% ± 3.91%; (mean ± SD)) and ≤ 17.4% (12.69% ± 4.08%), respectively.

Statistical analysis
SPSS (version 18.0) was used for data analysis. The results for continuous variables were expressed as mean ± SD; skewed distributions were presented as medians with interquartile ranges (IQR). Non-normally distributed variables were transformed to log or square root values. The relationship between sputum eosinophils and the surrogate markers were analysed using Pearson's correlation coefficient.

For the external validation-cohort receiver operating characteristic (ROC) curve analysis was performed for each variable individually or in combination, to determine the marker that best identified a sputum eosinophil count ≥ 3%. To analyse whether the area under the curve (AUC) of different ROC curves differ significantly, comparisons of AUCs were performed using R (version 2.15) and the pROC package(25). The best cut-off points were considered for each variable and sensitivity, specificity, positive predictive...
value (PPV) and negative predictive value (NPV) were calculated. In addition, sensitivity and specificity were calculated for alternative cut-offs that were previously published: blood eosinophils ≥ 0.25 $10^9$/L (15) and ≥ 0.22 $10^9$/L (26); FeNO levels < 24 ppb and > 50 ppb (27), and > 20 ppb (26); serum periostin levels > 25 ng/ml (19) and ≥ 50 ng/ml (28).

The diagnostic accuracy of the best predictive marker for sputum eosinophils in the external validation-cohort was subsequently verified in the replication-cohort using ROC curve analysis.

**RESULTS**

110 out of 200 patients in the external validation-cohort and 37 out of 40 patients in the replication-cohort were able to produce adequate sputum samples. The patient characteristics of both cohorts are described in Table 1, and characteristics stratified by sputum eosinophil counts of less than 3% or 3% and greater are presented in Table 2.

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>External validation cohort</th>
<th>Replication cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>110</td>
<td>37</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49 ± 13.8</td>
<td>37 ± 11.4</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>BMI</td>
<td>28 ± 5.2</td>
<td>30 ± 7.5</td>
</tr>
<tr>
<td>Smoking history (py)*</td>
<td>4 (0-18)</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Oral corticosteroids (%)</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Inhaled corticosteroids (%)</td>
<td>85</td>
<td>100</td>
</tr>
<tr>
<td>Dose ICS (µg/day)*</td>
<td>500 (250-500)</td>
<td>500 (500-1000)</td>
</tr>
<tr>
<td>Atopy (% positive RAST)</td>
<td>43</td>
<td>57</td>
</tr>
<tr>
<td>Total IgE (Ku/L)*</td>
<td>62 (26-235)</td>
<td>89 (80-106)</td>
</tr>
<tr>
<td>pb FEV₁ (% predicted)</td>
<td>100 ± 17.1</td>
<td>90 ± 18.5</td>
</tr>
<tr>
<td>pb FEV₁/FVC (% predicted)</td>
<td>95 ± 11.0</td>
<td>88 ± 15.5</td>
</tr>
</tbody>
</table>

Data expressed as mean ± standard deviation; *median (interquartile range); 1fluticason equivalent; pb=postbronchodilator

**External validity of blood eosinophils, FeNO and serum periostin**

Blood eosinophils and FeNO correlated with sputum eosinophil percentages ($r=0.59$, $p<0.001$ and $r=0.52$, $p<0.001$, resp.). There was no significant correlation between serum periostin and sputum eosinophil percentages ($r=0.09$, $p=0.4$).

The diagnostic accuracy of blood eosinophils, described as ROC AUC, was 89% ($p<0.001$, 95% CI: 0.81-0.96) (Figure 1). Using ≥0.27 $10^9$/L blood eosinophils as a cut-off,
Table 2. Patient characteristics stratified by sputum eosinophil percentages

<table>
<thead>
<tr>
<th></th>
<th>External validation cohort</th>
<th>Replication cohort</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild to moderate asthma</td>
<td>Moderate to severe asthma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EO ≥ 3% n=30</td>
<td>EO &lt; 3% n=80</td>
<td>EO ≥ 3% n=16</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52 ± 14.0</td>
<td>49 ± 13.6</td>
<td>55 ± 9.1</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>43</td>
<td>54</td>
<td>56</td>
</tr>
<tr>
<td>BMI</td>
<td>28 ± 5.3</td>
<td>28 ± 5.2</td>
<td>31 ± 9.3</td>
</tr>
<tr>
<td>Smoking history (py)*</td>
<td>6 (0-17)</td>
<td>4 (0-19)</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Dose ICS (µg/day)*³</td>
<td>500 (250-500)</td>
<td>250 (250-500)</td>
<td>500 (500-1000)</td>
</tr>
<tr>
<td>% positive RAST</td>
<td>60*</td>
<td>37*</td>
<td>50</td>
</tr>
<tr>
<td>Serum IgE (Ku/L)*⁴</td>
<td>164 (34-262)*</td>
<td>54 (20-190)*</td>
<td>226 (35-383)</td>
</tr>
<tr>
<td>pb FEV₁, % pred</td>
<td>101 ± 18.5</td>
<td>100 ± 16.6</td>
<td>86 ± 21.4</td>
</tr>
<tr>
<td>pb FEV₁/FVC, % pred</td>
<td>92 ± 9.5</td>
<td>96 ± 11.4</td>
<td>82 ± 15.3</td>
</tr>
<tr>
<td>Bl eosinophils, 10⁹/l²⁵</td>
<td>0.38 (0.29-0.61)**</td>
<td>0.14 (.09-0.20)**</td>
<td>0.33 (0.23-0.48)**</td>
</tr>
<tr>
<td>FeNO level, ppb⁷</td>
<td>55 (17-86)**</td>
<td>18 (13-32)**</td>
<td>—</td>
</tr>
<tr>
<td>Periostin, ng/mL⁸</td>
<td>27 (21.2-32.9)</td>
<td>25 (19.0-32.8)</td>
<td>42 (27.1-59.3)</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SD; * median (interquartile range); *t-test p<0.05, **t-test p<0.001
Abbreviations: Bl= blood; Dose ICS=fluticasone equivalent; pb=postbronchodilator; pbb= parts per billion

Figure 1. ROC curve analyses of the sensitivity and the specificity of blood eosinophils, FeNO and serum periostin for the diagnosis of eosinophilic inflammation in the external validation cohort. AUC = area under the curve.
eosinophilic and non-eosinophilic inflammation were well differentiated with a sensitivity of 78%, a specificity of 81% (table 3).

The overall accuracy of FeNO levels to differentiate eosinophilic and non-eosinophilic inflammation, described as ROC AUC, was 78% (p< 0.001, 95% CI: 0.66-0.89) (Figure 1). This ROC AUC was not significantly different from the ROC AUC of blood eosinophils (p=0.09). A FeNO level of ≥ 42 ppb provided a sensitivity of 63% and specificity of 92% (table 2).

Serum periostin was not able to distinguish eosinophilic from non-eosinophilic inflammation (ROC AUC= 55%, p=0.44, 95% CI: 0.43-0.67) (figure 1).

When combining these three variables in the prediction of eosinophilic inflammation no improvement was seen, resulting in an ROC AUC of 88 % (p<0.001, 95% CI: 0.79-0.97) (figure 1).

Since others have reported 2% sputum eosinophils as an alternative criterion for the diagnosis of eosinophilic or non-eosinophilic asthma(8), additional ROC curve analyses

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood eosinophils &gt; 0.22 10^9/L</td>
<td>86</td>
<td>79</td>
<td>86</td>
<td>80</td>
</tr>
<tr>
<td>Blood eosinophils ≥ 0.25 10^9/L</td>
<td>79</td>
<td>84</td>
<td>79</td>
<td>91</td>
</tr>
<tr>
<td>Blood eosinophils ≥ 0.27 10^9/L</td>
<td>78</td>
<td>81</td>
<td>79</td>
<td>91</td>
</tr>
<tr>
<td>FeNO level &gt; 20 ppb</td>
<td>74</td>
<td>57</td>
<td>74</td>
<td>61</td>
</tr>
<tr>
<td>FeNO level ≥ 24 ppb</td>
<td>74</td>
<td>63</td>
<td>74</td>
<td>63</td>
</tr>
<tr>
<td>FeNO level ≥ 42 ppb</td>
<td>63</td>
<td>92</td>
<td>63</td>
<td>92</td>
</tr>
<tr>
<td>FeNO level &gt; 50 ppb</td>
<td>56</td>
<td>92</td>
<td>52</td>
<td>92</td>
</tr>
</tbody>
</table>

PPV= positive predictive value; NPV= negative predictive value

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood eosinophils &gt; 0.22 10^9/L</td>
<td>83</td>
<td>82</td>
<td>83</td>
<td>84</td>
</tr>
<tr>
<td>Blood eosinophils ≥ 0.25 10^9/L</td>
<td>74</td>
<td>86</td>
<td>74</td>
<td>91</td>
</tr>
<tr>
<td>Blood eosinophils ≥ 0.27 10^9/L</td>
<td>69</td>
<td>92</td>
<td>69</td>
<td>92</td>
</tr>
<tr>
<td>FeNO level ≥ 20 ppb</td>
<td>76</td>
<td>60</td>
<td>76</td>
<td>63</td>
</tr>
<tr>
<td>FeNO level ≥ 24 ppb</td>
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<tr>
<td>FeNO level ≥ 42 ppb</td>
<td>58</td>
<td>94</td>
<td>58</td>
<td>94</td>
</tr>
<tr>
<td>FeNO level &gt; 50 ppb</td>
<td>48</td>
<td>94</td>
<td>48</td>
<td>94</td>
</tr>
</tbody>
</table>

PPV= positive predictive value; NPV= negative predictive value
were performed using 2% sputum eosinophils as cut-off. The results were similar to those using criterion of 3% sputum eosinophils, with an ROC AUC of 88% (p<0.001) for blood eosinophils, an ROC AUC of 79% (p<0.001) for FeNO and no significant diagnostic accuracy for serum periostin (Table 4).

Replication

In the replication cohort as well, there was a significant correlation between blood eosinophils and sputum eosinophil percentages (r=0.80, p<0.001). Blood eosinophil levels were effective in assessing eosinophilic inflammation, with an ROC AUC of 85% (p<0.001, 95% CI: 0.72-0.98) (figure 2). Using ≥0.27 \(10^9/\text{L}\) blood eosinophils as reported in the validation-cohort as best threshold, the sensitivity was 60% and specificity 90%. In line with the results of the external validation-cohort, no correlation was found between serum periostin and sputum eosinophils in the replication cohort (r=0.13, p=0.46), nor was periostin able to distinguish eosinophilic from non-eosinophilic inflammation (ROC AUC 54%, p=0.79, 95% CI: 0.34-0.74) (Figure 2).

**Figure 2.** Verification of findings: ROC curve analyses of the sensitivity and the specificity of blood eosinophils and serum periostin for the diagnosis of eosinophilic inflammation in the replication cohort with more severe asthma. AUC = area under the curve.
Discussion

This study shows that in patients with mild to moderate asthma blood eosinophils is an accurate surrogate marker for sputum eosinophils. Next, we were able to replicate blood eosinophils as highly effective surrogate marker in a second independent cohort of patients with more severe asthma. Serum periostin showed the lowest accuracy for eosinophilic asthma in both cohorts. These findings suggests that the blood eosinophil count can be used in mild, moderate and severe asthma as an easy to measure biomarker for sputum eosinophil percentage, which can have great practical advantages for guiding current or novel anti-inflammatory therapies.

Interestingly, blood eosinophils and sputum eosinophils were highly correlated in both our cohorts and exhibited the highest diagnostic accuracy, which validates previous data (26) except a very recent report in the Journal of Allergy and Clinical Immunology (18). We were not able to show a role for periostin as diagnostic marker for sputum eosinophils in both populations. The present data are not in line with the single previous study investigating the relationship between sputum eosinophils and all three markers (19), which demonstrated the highest ROC AUC for serum periostin.

In our study, FeNO appeared to be the second-best predictor for eosinophilic inflammation with an ROC AUC 0.78, which is nearly similar to previous studies(18;19;26), although surprisingly the best combination of sensitivity and specificity was achieved at a rather high cut-off level of 42 ppb in our cohort of patients with mild to moderate disease. Although FeNO was significant associated with sputum eosinophils, when combining the three markers in the ROC analysis both FeNO and periostin did not have additive value. This suggests that blood eosinophil count alone is the strongest independent predictor for eosinophilic inflammation.

To the best of our knowledge, this is the first study to externally validate serum periostin as surrogate marker for sputum eosinophils in a population of mild to moderate asthma, including replication in a second cohort with more severe disease. We believe that the strength of this study is that we have two independent well-characterised cohorts of varying asthma severity and treatment, though with similar stringent criteria for the diagnosis of asthma. The predictive accuracy of blood eosinophils is unlikely to be affected by treatment in our cohorts, since we recruited widely varying levels of therapy in mild, moderate and severe patients, including 19% of the severe patients using oral corticosteroids. Next, the sputum from both cohorts was processed in different, standardized ways (whole sample versus selected plug). Nevertheless, the correlation with blood eosinophils was consistent, which may be due to careful QC procedures. We used 3% sputum eosinophils as the threshold for eosinophilic or non-eosinophilic airway inflammation according to literature. Because others have used 2% as cut-off we re-analysed the data with 2% blood eosinophils as threshold, showing similar results.
One of the potential weaknesses of our study is that we could not obtain adequate sputum in all patients. However, no significant differences were found in blood eosinophil counts and FeNO level between the patients who successfully produced sputum and those who did not (data not shown). Therefore, we do not believe that the results of our study are biased by this limitation. Finally we have used a different assay to measure serum periostin as compared to previous studies. Our in-house ELISA for periostin was validated. The observed amounts of periostin in serum were similar to those reported before (19, 28) and therefore it is unlikely that the in-house ELISA failed to recognize the relevant isoforms of periostin. Therefore, we believe that the present results are not biased by inaccurate or unreliable measurements of serum periostin.

The correlation between blood and sputum eosinophils in asthma may not be biologically surprising. Eosinophils are produced in the bone marrow and in case of inflammation the formation is amplified and the eosinophils traffic into inflammatory sites, all under influence of a number of cytokines, such as IL-5(29). Blood eosinophils of patients with asthma have a distinct phenotype, especially in relation to their adhesive properties (30), which is involved in the transmigration across endothelium and epithelium. Increased eosinophils were observed in both blood and sputum after allergen challenge (31). Furthermore, several studies have demonstrated that the infusion of anti-IL-5 (mepolizumab) intravenously dramatically lowers eosinophil levels in both the blood and sputum or BALF (32-34). Hence, although the transport of eosinophils from the blood into the lung is a complex active process, in a chronic inflammatory disease such as asthma the levels of eosinophils in the blood and sputum appear to be closely related.

What are the clinical implications of our study? Since the measurement of blood eosinophils is easy and quick in comparison to sputum eosinophils, our data support the opportunity to assess the presence or absence of eosinophilic airway inflammation and monitor treatment in asthma. This is supported by a large study using anti-IL-5 (mepolizumab) to target eosinophilic airway inflammation in patients with severe asthma, in which blood eosinophil count in the previous year was predictive for the efficacy of reducing exacerbations (16).

In conclusion, we showed a strong relationship between blood eosinophils and sputum eosinophils in two independent cohorts with varying asthma severity. Serum periostin was not related to sputum eosinophils in mild to moderate asthma, and again this finding was replicated in the population with more severe disease. Our data indicate that blood eosinophils represent an accurate biomarker for sputum eosinophils in asthma, which can facilitate effective guidance of individualized asthma treatment.
References