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Early View

Research letter

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Eosinophilic cationic protein as marker for response to antibody therapy in severe asthma

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To the Editor:

As eosinophil granulocytes are the main effector cells in patients suffering from bronchial asthma [1], the introduction of anti-interleukin 5 (IL5) and IL5-receptor antibodies therapy led to a substantial change in severe asthma treatment [2,3]. Despite a correlation between eosinophils and response to antibody therapy is known, only few data regarding biomarkers and predicting factors for treatment outcome are available [4]. As eosinophil blood levels are influenced by oral and inhaled steroid therapy, we assumed that the dosage of eosinophilic cationic protein (ECP) might be a better biomarker to predict therapy response.

We conducted a retrospective, single center, cohort study at the Hannover Medical School (MHH), Germany, from May 2019 to November 2021. 80 patients were enrolled in the study, all 18 years or older and affected by severe eosinophilic asthma as defined by ERS guidelines [1]. Patients were treated according to guidelines with mepolizumab, benralizumab or dupilumab for at least 6 months. All patients provided informed written consent allowing the use of their data for scientific purposes, as approved by the Ethics Committee of Hannover Medical School (Ethics Committee Vote Nr. 10051_BO_K_2021). Data were collected prior to start of antibody treatment (baseline, T0), after 3 months (T1) and 6 months (T2) of therapy. According to treatment response criteria defined by Drick et al, 2018 [4], patients were divided in *responder* and *non-responder.* Two out of the three following criteria had to be fulfilled: improvement of subjective condition, gain in FEV1 at least 200 ml or 12% of predicted value and eosinophil count reduction to < 150/µL or less than 80% from the baseline value. Improvement of subjective condition included self-reported physical performance, symptoms control, quality of life and reduction of exacerbations. Baseline serum level of ECP was compared between *responder* and *non-responder* groups and correlated to the clinical outcomes. As eosinophil levels are known to be affected by oral corticosteroids, same analysis was conducted in patients not exposed to oral corticosteroids (OCS) at baseline. To minimize confounding factors on ECP, the analysis was conducted also among patients never exposed to smoke and among never smoker patients and not obese. The normal value for ECP was defined as lower than 13.3 µg/L, in concordance to the reference value of our laboratory.

Kolmogorov-Smirnov test was applied to all the continuous variables, and, depending on distribution, they were shown as mean ± standard deviation (SD) or median with interquartile ranges (IQR) unless indicated otherwise. For group comparisons, Fisher's exact test, Chi-squared test, two-sided Wilcoxon and Friedman´s tests were used, as appropriate. All reported p-values are two-sided. P-values < 0.05 were considered statistically significant.

Results were shown in table 1.

ECP was analyzed as a possible predictor of treatment response to antibody therapy, along with the absolute eosinophil count. Among the 59 responder patients, 27 (45.8%) had an ECP value ≥ 13.3 µg/L and

35 (59.3%) showed ≥ 300 eosinophils/µL at baseline, versus 8 (38.1%) non-responder patients (p=0.543) with an ECP value ≥ 13.3 and 10 (47.6%) patients with ≥ 300 eosinophils/µL, p=0.353. The Receiver Operating Characteristic (ROC) curve for clinical response showed an area under the curve (AUC) of 54.4% for ECP and 54.1% for eosinophil count. AUC curves were similar for each drug group. For patients without OCS therapy (n=31), 23 were classified as responders (74.2%). Among them, 13 (56.5%) had an ECP value ≥ 13.3 µg/L versus 1 (12.5%) non-responder (p=0.045) whereas 18 (78.3%) showed ≥ 300 eosinophils/µL versus 4 (50.0%, p=0.185), see Table 1.

This is the first study that evaluates the clinical relevance of ECP compared to serum eosinophils levels in patients with severe eosinophilic asthma regarding treatment response criteria. In a group of 20 patients treated with mepolizumab, Kobayashi et al demonstrated a reduction of ECP levels [5] and a correlation between FEV1 improvement and ECP levels. A similar reduction of ECP levels was described in patients treated with benralizumab [6]. In line with these findings, in this study, both the eosinophil count and the ECP values declined after initiation of therapy. As high ECP levels correlate with more severe asthma, it was judged as a marker of disease severity by Badar and colleagues [7]. They and other authors found a negative correlation between serum ECP and FEV1 and FEV1/FVC [8,9]. In contrast to previous studies, ECP demonstrated no correlation with FEV1 or ACT score in our cohort. The explanation could be, that all the previous studies compared asthmatic patients and healthy controls, while our population was composed entirely by severe asthmatic patients. To sum up, ECP serum levels do not better correlate with clinical outcomes than absolute counts of eosinophils except for OCS-free asthmatic patients, in which higher levels of ECP have superior predictive value for therapy response. Our results proved that ECP levels were influenced by oral corticosteroid therapy like serum eosinophil levels [10]. In this real life cohort, not only OCS therapy at baseline could influence outcome, even smoking history or obesity could negatively impact on outcome. That is why subgroups analysis were performed (not shown in detail) an no differences in baseline ECP or eosinophil level were found.

Finally, we conclude that ECP measurement in OCS free patients may be used as response predictor but more research is needed so far. Considering the whole severe eosinophilic asthmatic population, ECP values are not a more useful tool than the number of eosinophils.

Take home message

We studied the Eosinophil Cationic Protein (ECP) as predictor of clinical response to biological therapy in severe asthma. We found that ECP is not useful in non-selected patients but may have a role in those not exposed to oral corticosteroids.

Declarations

Ethics approval and consent to participate: this study was approved by the Ethics Committee of Hannover Medical School (Ethics Committee Vote Nr. 10051_BO_K_2021).

Consent for publication: not applicable

Availability of data and materials: the datasets generated during and/or analyzed during the current study are available from the corresponding author upon individual and specific request. The use of individual data of patients outside specific personal consultation will not be permitted.

Competing interests: the authors declare that they have no competing interests

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Table 1. Patient characteristics and response to therapy

	Total (n 80)			
Male sex, n (%)	36 (45.0%)			
Age, years median (IQR)	58 (50-67)			
BMI, median (IQR)	27.1 (24.1-32.2)			
BMI ≥ 30), n (%)	28 (35.0%)			
Smoking history (pack years), median (IQR)	11.5 (4.3-25.8)			
Atopic dermatitis, n (%)	9 (11.3%)			
Chronic rhinosinusitis with nasal polyps, n (%)	4 (5.0%)			
Mepolizumab Benralizumab Dupilumab	36 (45.0%) 27 (33.7%) 17 (21.3%)			
Comparison across the timeline	**T0**	**T1**	**T2**	**p value**
FEV1 (% predicted), median (IQR)	63 (48-83)	73 (55-86)	70 (55-86)	0.028$^{\pm}$
Eosinophil serum absolute value (n/µL),	345 (120-610)	40 (0-110)	40 (0-133)	<0.001$^{\pm}$

median (IQR)				
ACT score, median (IQR)	13 (10-16)	17 (13-21)	16 (13-21)	<0.001[±]
ECP serum value (µg/L), median (IQR)	11.8 (6.1-19.3)	7.1 (5.1-10.3)	-	< 0.001[◊]
Outcome	**Responders (n 59)**	**Non-responders (n 21)**		
ECP serum value ≥ 13.3 µg/L, n (%)	27 (45.8%)	8 (38.1%)		0.543[⍰]
Eosinophil count ≥ 300/µL, n (%)	35 (59.3%)	10 (47.6%)		0.353[⍰]
OCS-free patients n 31	**Responders (n 23)**	**Non-responders (n 8)**		
ECP serum value ≥ 13.3 µg/L, n (%)	13 (56.5%)	1 (12.5%)		0.045[†]
Eosinophil count ≥ 300/µL, n (%)	18 (78.3%)	4 (50.0%)		0.185[†]

IQR: Interquartile Range; BMI. Body Mass Index; OCS: Oral Corticosteroids; ECP: eosinophil cationic protein; ACT: Asthma Control Test; FEV1: Forced Expiratory Volume in First Second.
[±] Friedman´s two ways analysis of variance; [◊] Wilcoxon Matched-Pair test; [⍰]chi square test; [†]Fisher's exact test

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