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

Received: 20 March 2022
Accepted: 3 June 2022

To the Editor:

As eosinophil granulocytes are the main effector cells in patients suffering from bronchial asthma [1], the introduction of anti-interleukin (IL)-5 and IL-5 receptor antibodies therapy led to a substantial change in severe asthma treatment [2, 3]. Despite a correlation between eosinophils and response to antibody therapy, little 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-centre, 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 and affected by severe eosinophilic asthma as defined by European Respiratory Society 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 MHH (Ethics Committee vote number 10051_BO_K_2021). Data were collected prior to start of antibody treatment (baseline), and after 3 months and 6 months of therapy. According to treatment response criteria defined by Drick *et al.* [4], patients were divided into "responders" and "nonresponders". Two out of the three following criteria had to be fulfilled: improvement of subjective condition; gain in forced expiratory volume in 1 s (FEV_1) ⩾200 mL or 12% of predicted value; and eosinophil count reduction to <150 per µL or <80% from the baseline value. Improvement of subjective condition included self-reported physical performance, symptom control, quality of life and reduction of exacerbations. Baseline serum level of ECP was compared between the responder and nonresponder groups and correlated to the clinical outcomes. As eosinophil levels are known to be affected by oral corticosteroids (OCS), the same analysis was conducted in patients not exposed to OCS at baseline. To minimise confounding factors on ECP, the analysis was conducted also among patients never exposed to smoke, and among never-smoker patients and those who were not obese. The normal value for ECP was defined as <13.3 $\mu g \cdot L^{-1}$, in concordance to the reference value of our laboratory.

The Kolmogorov–Smirnov test was applied to all the continuous variables, and, depending on distribution, they are presented as mean± SD or median (interquartile range) unless otherwise indicated. 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 are shown in table 1.

ECP was analysed 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 $\mu g \cdot L^{-1}$ and 35 (59.3%) showed ⩾300 eosinophils per µL at baseline, *versus* eight (38.1%) nonresponder patients (p=0.543) with an ECP value ⩾13.3 $\mu g \cdot L^{-1}$ and 10 (47.6%) patients with ⩾300 eosinophils per µL (p=0.353). The receiver operating characteristic curve for clinical response showed an area under the curve (AUC) of 54.4% for ECP and 54.1% for eosinophil count. AUCs 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 $\mu g \cdot L^{-1}$ *versus* one (12.5%) nonresponder (p=0.045) whereas 18 (78.3%) showed ⩾300 eosinophils per µL *versus* four (50.0%) (p=0.185) (see table 1).

Shareable abstract (@ERSpublications)
This study of the eosinophil cationic protein (ECP) as predictor of clinical response to biological therapy in severe asthma found that ECP is not useful in unselected patients but may have a role in those not exposed to oral corticosteroids. https://bit.ly/398RwEk

Cite this article as: Franceschi E, Drick N, Fuge J, *et al*. Eosinophilic cationic protein as marker for response to antibody therapy in severe asthma. *ERJ Open Res* 2022; 8: 00138-2022 [DOI: 10.1183/23120541.00138-2022].

TABLE 1 Patient characteristics and response to therapy

Patients n				80
Male sex				36 (45.0%)
Age, years				58 (50–67)
BMI, kg·m^{-2}				27.1 (24.1–32.2)
BMI ⩾30 kg·m^{-2}				28 (35.0%)
Smoking history, pack-years				11.5 (4.3–25.8)
Atopic dermatitis				9 (11.3%)
Chronic rhinosinusitis with nasal polyps				4 (5.0%)
Mepolizumab				36 (45.0%)
Benralizumab				27 (33.7%)
Dupilumab				17 (21.3%)
Comparison across the timeline	**t_0**	**t_1**	**t_2**	**p-value**
FEV$_1$, % predicted	63 (48–83)	73 (55–86)	70 (55–86)	0.028[¶]
Eosinophil serum absolute value, per µL	345 (120–610)	40 (0–110)	40 (0–133)	<0.001[¶]
ACT score	13 (10–16)	17 (13–21)	16 (13–21)	<0.001[¶]
ECP serum value, µg·L^{-1}	11.8 (6.1–19.3)	7.1 (5.1–10.3)		<0.001[+]
Outcome	**Responders**	**Nonresponders**		**p-value**
Patients n	59	21		
ECP serum value ⩾13.3 µg·L^{-1}	27 (45.8%)	8 (38.1%)		0.543[§]
Eosinophil count ⩾300 per µL	35 (59.3%)	10 (47.6%)		0.353[§]
OCS-free patients[#]	**Responders**	**Nonresponders**		**p-value**
Patients n	23	8		
ECP serum value ⩾13.3 µg·L^{-1}	13 (56.5%)	1 (12.5%)		0.045[f]
Eosinophil count ⩾300 per µL	18 (78.3%)	4 (50.0%)		0.185[f]

Data are presented as median (interquartile range) or n (%) unless otherwise stated. BMI: body mass index; t_0: baseline; t_1: 3 months; t_2: 6 months; FEV$_1$: forced expiratory volume in 1 s; ACT: Asthma Control Test; ECP: eosinophil cationic protein; OCS: oral corticosteroids. [#]: n=31; [¶]: Friedman's two-way ANOVA; [+]: Wilcoxon matched-pair test; [§]: Chi-squared test; [f]: Fisher's exact test.

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.* [5] demonstrated a reduction of ECP levels and a correlation between FEV$_1$ 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 to be a marker of disease severity by Badar *et al.* [7]. They and other authors found a negative correlation between serum ECP, and FEV$_1$ and FEV$_1$/forced vital capacity [8, 9]. In contrast to previous studies, ECP demonstrated no correlation with FEV$_1$ or Asthma Control Test 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 of severe asthmatic patients. To summarise, serum ECP levels do not correlate better with clinical outcomes than absolute counts of eosinophils except for in OCS-free asthmatic patients, in whom higher levels of ECP have superior predictive value for therapy response. Our results show that ECP levels are influenced by OCS 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 subgroup analysis was performed (not shown in detail) and 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. Considering the whole severe eosinophilic asthmatic population, ECP values are not a more useful tool than the number of eosinophils.

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Provenance: Submitted article, peer reviewed.

Author contributions: Conceptualisation and project administration: H. Suhling, N. Drick and T. Welte; data collection: H. Suhling and E. Franceschi; methodology and data analysis: E. Franceschi and J. Fuge. All authors discussed the results and contributed to writing, review and editing. All authors read and approved the final manuscript.

Ethics approval: This study was approved by the Ethics Committee of Hannover Medical School (ethics committee vote number 10051_BO_K_2021).

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

Conflict of interest: The authors declare that they have no competing interests

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