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Scientific letter

Eosinophil and Cationic Protein Levels in Patients Treated With Dupilumab: A Real-Life Study

Conteo de eosinófilos y proteína catiónica del eosinófilo en pacientes tratados con dupilumab: un estudio en vida real

Dear Editor,

Dupilumab is an effective and safe treatment for severe uncontrolled asthma (SUA), chronic rhinosinusitis (CRS), nasal polyposis (NP), and moderate-to-severe atopic dermatitis.[1–5] Eosinophilia, reported in 4–14% of patients, is a common but usually transient side effect of dupilumab that rarely requires treatment discontinuation due to its minimal clinical impact.[2,5,6] It has been suggested that dupilumab-induced eosinophilia might not be associated with increased eosinophil activity. Eosinophil activity can potentially be assessed through eosinophil cationic protein (ECP), a protein stored in eosinophil granules and released during activation or degranulation, which can be readily measured in blood.[7,8] Therefore, the primary objectives of this study were to evaluate changes in clinical variables related to SUA and/or CRSwNP, as well as alterations in blood eosinophil count (BEC) and ECP levels, following one year of dupilumab treatment in a real-life setting.

We conducted a single-center, observational, retrospective observational study at La Paz University Hospital in Madrid, Spain. The study protocol was approved by the local ethics committee (PI-2932). Patients aged 18 years or older who had received dupilumab for SUA (600 mg initially, followed by 300 mg every two weeks) for at least one year were included.

All included patients are followed in a multidisciplinary severe asthma unit, and all met the criteria for dupilumab initiation according to GEMA guidelines.[9] All patients who had previously been treated with an anti-IL5 complied with a washout period of at least 2 months.

SUA was defined when the disease remains poorly controlled despite receiving treatment in the last year with a combination of High-dose inhaled corticosteroids, Long-acting β_2-agonists, Long-acting anticholinergics or when there is a requirement for maintenance systemic corticosteroids lasting 6 months per year regardless of the dose, or a cumulative dose exceeding 1 gram of prednisone or equivalent, regardless of the duration.[10] Demographic data, T2 comorbidities (CRS and/or NP), number of exacerbations, pulmonary function test results, asthma control test (ACT) scores, asthma quality of life questionnaire (AQLQ) scores, scales assessing the control of nasosinusal-symptoms as well as BEC, serum immunoglobulin E (IgE), and ECP levels were collected at baseline and after 12 months of treatment. Data were analyzed using R Core Team software (2024). Quantitative variables were expressed as medians and interquartile ranges, depending on their distribution. A p-value of <0.05 was considered statistically significant.

We included 35 patients with T2 SUA. Fifty-four percent were men, with a median age of 52 years (IQR: 36.5–60 years). Among the participants, 46% had conjunctivitis, 77% rhinosinusitis and 60% nasal polyposis (NP). Additionally, 57.1% were receiving systemic corticosteroids, and 28.6% were on anti-IL-5 therapy for asthma. Baseline clinical characteristics are summarized in Supplementary Material.

In the analysis of baseline characteristics, no significant differences were found between groups in variables such as early asthma onset, smoking history, bronchiectasis, gastroesophageal reflux, obesity, anxiety or depression, or asthma control measures (ACT, AQLQ, FEV_1, FeNO, and the number of exacerbations requiring corticosteroids or antibiotics). However, a significant difference was observed in the mean number of nasal polyp (NP) surgeries between patients with nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD) and those without N-ERD (2.08 vs. 0.45; $p < 0.005$).

After one year of dupilumab treatment, we observed statistically significant improvements in several parameters, including median ACT, mean SNOT-22, median FeNO, and median total IgE levels, as well as reductions in oral corticosteroid use for asthma and olfactory alterations. Additionally, there was a statistically significant increase in median VAS and mean FEV_1 (%).

Regarding BEC and ECP levels, no statistically significant changes were observed after dupilumab treatment ($p = 0.06$ and $p = 0.17$, respectively). However, a significant correlation was noted between BEC and allergic eosinophilic asthma ($p = 0.036$), which was not observed between ECP levels and this asthma phenotype ($p = 0.195$). Regarding the rest of the variables studied, no statistically significant correlations were found for either BEC or ECP. Follow-up clinical data are provided in Table 1.

Our study demonstrates significant improvement in nearly all asthma and CRSwNP outcome variables after one year of dupilumab treatment, except for the VAS score for nasosinusal symptoms, which showed a significant increase. These findings are consistent with previously published studies. Caminati et al. conducted a prospective study involving 195 patients with asthma, asthma with CRSwNP, and Samter-Widal triad, all treated with dupilumab (300 mg every two weeks) for 12 months. Their results indicated significant improvements in asthma outcomes (FEV_1, ACT score, FeNO, and OCS use) as well as in polyposis outcomes (SNOT-22 and VAS scores).[11] Similarly, Pelaia et al. performed a retrospective multicenter observational study of patients with T2 severe asthma (61.4% with CRSwNP) treated with dupilumab (300 mg every two weeks) for six months. They reported significant improvements in ACT scores, number of exacerbations, FEV1 (in liters and percentages), FeNO, and SNOT-22 scores.[12] Ledda et al. conducted a prospective real-life observational study of 21 patients with

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Table 1
Follow-up clinical data.

	Overall population ($n = 35$)		
	Baseline	12 months post Dupilumab	*p* value
Asthma outcomes			
ACT score, median, (IQR)	19 (16.0–22.0)	22 (20.3–23.0)	0.003
Exacerbations requiring systemic corticosteroids, median, (IQR)	1 (0–2.0)	0 (0–0)	0.005
Oral prednisone equivalent dose (mg) median, (IQR)	412 (278.0–512.0)	450 (256–1350)	0.17
FEV1 (ml), mean (SD)	2615 (±900.6)	2700 (±1256.9)	0.78
FEV1 percent predicted, mean (SD)	81.3 (±21.0)	87.2 (±20.6)	0.03
FeNO (ppb), mean (SD)	40 (±43.2)	22 (±26.9)	0.001
Oral corticosteroid for asthma control, *n* (%)	20 (57.1%)	8 (22.9%)	0.02
CRSwNP outcomes			
SNOT-22, mean (SD)	44.4 (±19.11)	31.4 (±19.2)	0.01
VAS, mean (SD)	60 (±22.5)	77.5 (±28.0)	0.02
Alteration of smell, *n* (%)	19 (54.3%)	8 (22.9%)	0.02
Laboratory outcomes			
BEC, median, (IQR)	380 (250.0–480.0)	515 (212.5–697.5)	0.06
ECP, median, (IQR)	55 (29.9–98.7)	78 (38.4–127.8)	0.18
Total IgE, median, (IQR)	286 (155.0–865)	45 (19.3–150.5)	<0.001

ACT: asthma control test; AQLQ: asthma quality of life questionnaire; BEC: blood eosinophil count; CRSwNP: chronic rhinosinusitis with nasal polyposis; ECP: eosinophilic cationic protein; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 second; IQR: interquartile range; ml: milliliters; mg: milligrams; ppb: part per billion; SD: standard deviation; SNOT-22: sino-nasal outcome test 22; VAS: visual analogic scale; %: percentage.

CRSwNP (80.9% asthmatic) treated with dupilumab (300 mg every two weeks) for 10 months. They observed significant improvements in SNOT-22 scores, FeNO, and FEV1%, but no significant changes in ACT scores, noting that most patients were non-severe asthmatics with CRSwNP and often had normal baseline ACT scores.[13]

Although we observed a nearly significant increase in eosinophils ($p = 0.06$), no increase in ECP was observed after one year of treatment ($p = 0.18$; Table 1). These findings align with other published studies. Ledda et al. reported increases in BEC and ECP levels without statistical significance, as well as a significant decrease in IgE levels.[13] In another study by Sarnoch et al., involving 104 patients with CRSwNP (83% asthmatic) treated with dupilumab (300 mg every two weeks) for 13 months, a slight increase in BEC levels was observed, with no substantial change in ECP levels and an increase in IgE levels.[14] However, Sarnoch et al. did not conduct bivariate analysis, making it unclear whether the observed differences in BEC and IgE levels were statistically significant.[14] Despite the fact that ECP levels are associated with more severe asthma, there is ongoing controversy over whether serum ECP levels correlate better with clinical outcomes than absolute eosinophil counts, except in OCS-free asthmatic patients.[15] Our findings suggest that the increases in BEC and ECP levels did not compromise the effectiveness of dupilumab, consistent with the results of the aforementioned studies.

Furthermore, we observed a significant correlation between BEC and allergic eosinophilic asthma ($p = 0.036$), whereas no such correlation was found between ECP levels and this asthma phenotype. This result suggests that the hyper-eosinophilia frequently observed following dupilumab treatment does not necessarily indicate elevated eosinophil activity. This evidence supports the conclusion that the positive clinical outcomes and response to dupilumab observed in our study, as presented in Table 1, are likely associated with the suppression of eosinophil activity. However, further studies are needed to confirm this hypothesis.

Although our findings provide valuable insights into dupilumab's effectiveness in routine clinical practice, our study has important limitations: it is a real-life retrospective study with a small sample size and no control group, which represents a potential data loss. However, as previously mentioned, our study is based on real-life data and, in contrast to multicentric studies or clinical trials that rely on international registries, where selection bias may arise due to variability in the criteria used to initiate biological treatments across centers or countries, our study was conducted in a multidisciplinary, specialized pulmonology department within a single hospital, employing strict criteria for the prescription of biological treatments. This generally results in less variability in patient inclusion, thereby enhancing the robustness of the study.

In conclusion, treatment with dupilumab in patients with SUA and/or CRSwNP significantly improves nasosinusal symptoms, asthma control, corticosteroid use, and lung function after one year. Although a non-significant increase in eosinophils and ECP levels was observed, these changes do not appear to affect the efficacy of dupilumab.

Declaration

We declare that this manuscript has not been previously published and is not under consideration for publication in other journals. The manuscript has been read and approved by all authors and they certify that they have participated to an extent that they are willing to assume public responsibility for the content of the manuscript, complying with the authorship criteria recommended by the International Committee of Medical Journal Editors.

Ethical considerations

The study was approved by the Ethics Committee of Hospital Universitario La Paz (PI-2932), and all patients provided written informed consent prior to their inclusion, in accordance with the Declaration of Helsinki.

Generative AI

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Authors' contributions

MACR, JCB: conceptualization, investigation, writing – original draft, data extraction, data curation, methodology, formal analysis, validation. DL, FA: writing – review & editing, visualization, validation. EV, DR, SQ, JDO: conceptualization, writing – review & editing, supervision, methodology, validation.

Conflict of interest

The authors also report no conflicts of interest that could have influenced the outcomes or their interpretation.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.opresp.2025.100444.

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