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RESEARCH NOTE

Early increase in eosinophil count may predict long-term hypereosinophilia during dupilumab treatment: a 2-year observational study

Andrea Rampi MD[1,2] | **Umberto Tanzini MD**[1,2] | **Alessandro Vinciguerra MD**[3] | **Giulia Danè MD**[1] | **Luca Moroni MD**[2,4] | **Mona-Rita Yacoub MD**[4] | **Matteo Trimarchi MD**[1,2,5]

[1]Otorhinolaryngology Unit, Division of Head and Neck department, IRCCS San Raffaele Scientific Institute, Milan, Italy

[2]School of Medicine, Vita-Salute San Raffaele University, Milan, Italy

[3]Otorhinolaryngology and Skull Base Center, AP-HP, Hospital Lariboisière, Paris, France

[4]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy

[5]Department of Otolaryngology-Head and Neck Surgery, Ente Ospedaliero Cantonale, Ospedale Regionale di Lugano – Università della Svizzera Italiana, Lugano, Switzerland

Correspondence
Matteo Trimarchi, MD, Department of Otolaryngology-Head and Neck Surgery, Ente Ospedaliero Cantonale, Ospedale Regionale di Lugano – Università della Svizzera Italiana, Lugano, Switzerland.
Email: matteotrimarchi@gmail.com

KEYWORDS
chronic rhinosinusitis, eosinophilic rhinitis and nasal polyposis, paranasal sinus diseases, therapeutics

Key points

1. In a limited subset of patients, dupilumab-induced hypereosinophilia is persistent.
2. Two-month follow-up eosinophil count may predict long-lasting hypereosinophilia.

1 | INTRODUCTION

Dupilumab has transformed the clinical management of chronic rhinosinusitis with nasal polyps (CRSwNP) since 2019. This monoclonal antibody, targeting the interleukin (IL) 4 and IL-13 pathways, has in fact provided outstanding results in efficacy and safety.[1–4] Thus, an increase in the absolute eosinophil count (AEC) has been observed and widely described as a transient effect resolving within the first few months of therapy. This phenomenon is almost invariably devoid of clinical significance, but, in rare cases, eosinophil-induced organ damage has been observed, suggesting the need to find predictors of its onset and to monitor the condition.[5,6]

2 | METHODS

We present the results of eosinophil counts from a prospective, single-center study on patients who were prescribed dupilumab for CRSwNP at the Ear, Nose, and Throat Department of San Raffaele Hospital, Milan, from February 2021 to February 2023. The study was approved by the hospital's ethics committee (protocol code 112/INT/2021).

Dupilumab (300 mg every 2 weeks) was prescribed according to European Position Paper on Rhinosinusitis and Nasal Polyps 2020 criteria,[7,8] after thorough multidisciplinary examination to exclude other underlying conditions. Data were collected on demographics, comorbidities, endoscopic findings, and blood tests. Dupilumab was not prescribed if AEC was ≥ 1.5 ($\times 10^9$/L, as hereafter implied).

Follow-up (FU) visits were performed at approximately 2, 4, 6, 9, 12, 16, 20, and 24 months; IgE and cell blood counts (CBCs) were required at all visits, and, according to a previous study by our group,[6] patients with an AEC between 1.5 and 3.0 were more closely monitored (with monthly CBC measurement), while those reaching an AEC ≥ 3.0 were prescribed a short-term course of oral corticosteroids.

Statistical analyses were performed with SPSS version 24 (IBM) using Student *t* or chi-square test.

TABLE 1 Summary of the demographic and anamnestic features of the 60 patients.

	Mean (SD) or percentage
Age (years)	52.05 (12.25)
Weight (kg)	72 (12.85)
Height (m)	1.71 (0.1)
BMI (kg/m^2)	24.45 (2.84)
Men	61.7
Atopy[a]	52.8
Asthma[b]	78.3
Late-onset asthma[c]	30.6
N-ERD	41.7
Current or past smoker	48

Abbreviations: BMI, body mass index; N-ERD, nonsteroidal anti-inflammatory drug–exacerbated respiratory disease; SD, standard deviation.

[a]Patients were asked about their potential atopic condition, but not all underwent prick tests or specific IgE in the absence of symptoms. For this reason, this condition may be underestimated.

[b]Patients having the criteria for the prescription of dupilumab for both severe asthma and chronic rhinosinusitis with nasal polyps (CRSwNP) were not included in the present study, as they were given a doubled first dose (as per asthma regimen).

[c]Defined as first diagnosis ≥ 40 years, considering only patients with asthma.

3 | RESULTS

A total of 60 patients were included; pretherapy details are displayed in the Table 1. As patients started treatment at different time points, 60, 57, 50, 37, 25, 21, 18, and four patients reached 2, 4, 6, 9, 12, 16, 20, and 24 months of FU, respectively.

Before therapy, the mean AEC was 0.54; during FU, 13 patients (22%) had an AEC ≥ 1.5 at least once, and, among these, four (6.8%) reached the 3.0 threshold. In four of the 25 patients reaching 1-year FU (16%), an AEC ≥ 1.5 was detected after at least 12 months, later referred to as "long-lasting hypereosinophilia" (Figure 1). In all cases, hypereosinophilia had no clinical significance, except for one patient with slight worsening of asthma corresponding to an increase in AEC ≥ 3.

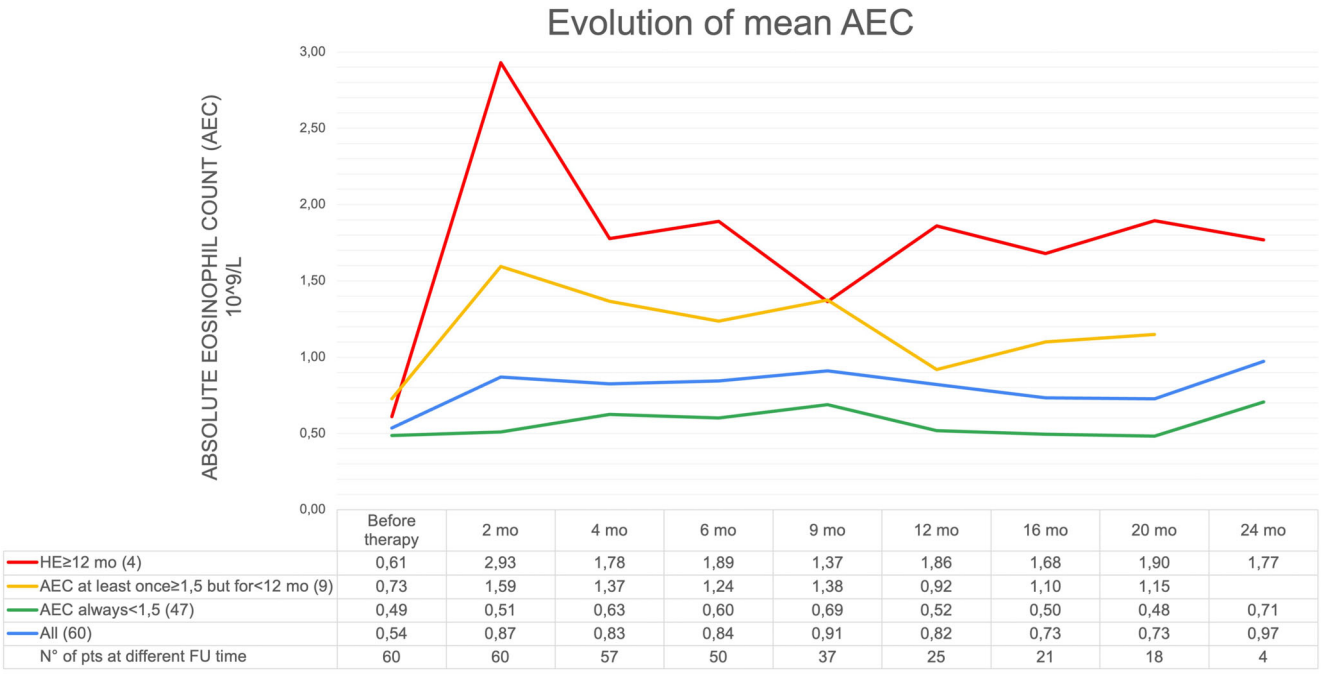
Age, sex, smoking, body mass index, asthma or nonsteroidal anti-inflammatory drug–exacerbated respiratory disease, total IgE count, and atopy were not significantly correlated with either the development of hypereosinophilia or long-lasting hypereosinophilia ($p > 0.05$).

The mean pretherapy AEC was higher in patients subsequently developing AEC ≥ 1.5 (0.53 vs 0.61; standard deviation, 0.25 and 0.23, respectively [$p = 0.006$]), while no statistically significant association was found with long-lasting hypereosinophilia.

The value of the AEC at 2 months was instead a valuable predictor of long-lasting hypereosinophilia (calculated in patients with FU ≥ 1 year): a value ≥ 3.0 was found to be a risk factor, while an AEC < 1.5 was identified as protective. In both cases, the correlation was statistically significant with a strong association ($p < 0.001$, Cramer V 0.84 and $p = 0.001$, Cramer V 0.70, respectively).

4 | DISCUSSION

The present study confirms that an increase in AEC is frequent during therapy with dupilumab, with a proportion slightly higher (22%) than in the SINUS trials.[1] Our findings, thus, support the long-lasting persistence of this laboratory test abnormality: in a significant percentage of patients (all experiencing hypereosinophilia during the first year), an AEC ≥ 1.5 was also detected at 12 months or later. This represents an original finding since, even if this was noted in some registrational studies,[9] only sporadic cases of long-lasting hypereosinophilia have been described in real-life, while the percentage in our cohort is significant (although on a limited sample) and suggests considering it as a constant condition in a subset of patients. It is worth specifying that different studies reported that the median value of AEC was stable during FU (even if the mean AEC



	Before therapy	2 mo	4 mo	6 mo	9 mo	12 mo	16 mo	20 mo	24 mo
HE≥12 mo (4)	0,61	2,93	1,78	1,89	1,37	1,86	1,68	1,90	1,77
AEC at least once≥1,5 but for<12 mo (9)	0,73	1,59	1,37	1,24	1,38	0,92	1,10	1,15	
AEC always<1,5 (47)	0,49	0,51	0,63	0,60	0,69	0,52	0,50	0,48	0,71
All (60)	0,54	0,87	0,83	0,84	0,91	0,82	0,73	0,73	0,97
N° of pts at different FU time	60	60	57	50	37	25	21	18	4

FIGURE 1 Evolution of the mean absolute eosinophil count (AEC) during follow-up in different subgroups: all patients (blue line, 60 patients); those never experiencing AEC ≥ 1.5 (green line, 47 patients); patients with AEC at least once ≥1.5 but resolving within 1 year (yellow line, nine patients); and cases with hypereosinophilia (HE) lasting ≥12 months (red line, four patients).

increased), advising that hypereosinophilia may affect specific patients.[1,9] As shown in the Figure 1, this finding seems to be confirmed in our cohort, since patients never reaching an AEC of 1.5 had a stable eosinophil count.

Our study could not detect a link between demographic features, body mass index, or type 2 comorbidities and the development of hypereosinophilia or long-lasting hypereosinophilia; the reasons for the predisposition to hypereosinophilia are therefore still obscure, but our analysis suggests that this propensity is detectable early during FU, 2 months after the first injection. Specifically, patients reaching the 3.0 threshold had a significantly higher risk of developing long-lasting hypereosinophilia, while a value < 1.5 appeared to be protective (Cramer V 0.84 and 0.70, respectively).

In addition, pretherapy AEC was higher in patients who subsequently developed AEC ≥ 1.5 (0.53 vs 0.61, $p = 0.006$). This finding is particularly interesting when compared with other recent evidence: a review of the registrational studies for all indications by Wechsler et al.[9] found that pretherapy AEC > 0.5 is a risk factor for hypereosinophilia during the study; in a still uncertain field, these are valuable data for a frequently developing condition. The same review by Wechsler et al.,[9] in fact, found a peak in AEC > 1.5 and >3.0 in up to 14% and 3.9% of patients, respectively (even more with corticosteroid tapering)[10]; thus, hypereosinophilia reaches clinical significance in only a minimal fraction of cases.

Moreover, AEC alone is probably insufficient to reliably predict the development of hypereosinophilia, while new markers are required; similarly, the value of 1.5 is widely recognized, but it does not constitute a solid safe/risk line. In this uncertain scenario, some authors have suggested monitoring CBC, while others advised further assessments only in the event of symptoms.[4–6] Accordingly, the identification of a subpopulation that is more prone to hypereosinophilia would allow tailored FU according to the patient's specific risk with more efficient allocation of resources.

The present data need to be confirmed, as the limited number of patients reduces the possibility to draw definite conclusions. Notwithstanding, this is the first real-life study to describe long-lasting dupilumab-induced hypereosinophilia in a prospective manner. Our findings suggest that 2-month eosinophil count may play an essential role in clinical practice.

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CONFLICT OF INTEREST STATEMENT

Matteo Trimarchi declares honoraria as a speaker from Sanofi, GlaxoSmithKline, and Novartis. Luca Moroni declares honoraria as a speaker and advisory boarding from GlaxoSmithKline and AstraZeneca. Mona-Rita Yacoub declares honoraria as a speaker from AstraZeneca, GlaxoSmithKline, Novartis, and Sanofi. The other authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ORCID

Andrea Rampi MD https://orcid.org/0000-0002-4952-5348
Matteo Trimarchi MD https://orcid.org/0000-0001-6472-3484

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