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CASE REPORT

Eosinophilic Organ Complications Associated with Dupilumab Therapy – Narrative Review and Current Evidence

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Background: Dupilumab is a monoclonal antibody targeting the interleukin (IL) 4 receptor alpha subunit. By inhibiting IL-4 and IL-13 signaling, it has shown efficacy in treating type 2 high inflammatory diseases. While generally well-tolerated, rare eosinophilic adverse events have been reported.

Methods: A narrative literature search was conducted using MEDLINE, Google Scholar, and Cochrane Central Register of Controlled Trials databases up to September 6, 2025. We searched for published cases of dupilumab-induced hypereosinophilia with organ involvement. Furthermore, we present data from the WHO Global Pharmacovigilance Database, VigiBase, using information component (IC) metrics.

Results: A 64-year-old woman with severe asthma, aspirin-exacerbated respiratory disease, and chronic rhinosinusitis with nasal polyposis developed nine months after dupilumab initiation recurrent eosinophilic pleural effusions (EPE), accompanied by peripheral eosinophilia (2520 cells/μL). Symptoms resolved only after dupilumab discontinuation. Our review includes 52 cases of dupilumab-associated eosinophilic adverse events. Most presented within three months of treatment initiation. Eosinophilic pneumonia (EP), eosinophilic granulomatosis with polyangiitis (EGPA) and hypereosinophilic syndrome (HES) were the most frequent reported manifestations. Although most patients recovered with dupilumab withdrawal and oral corticosteroids, clinical outcomes varied, and re-challenge was associated with a high recurrence rate. Analysis of VigiBase revealed significant values for a disproportionate frequency of reports of several eosinophilic adverse events (EGPA: IC025 +3.4; HES: IC025 +2.8; EP: IC025 +2.6, EPE: IC025 +2.2) in association with dupilumab.

Conclusion: Clinically significant eosinophilic adverse events during dupilumab therapy, though rare, can occur even after prolonged treatment periods. Long-term vigilance for eosinophil-mediated organ damage is important and for individualized risk-benefit assessments in patients receiving IL-4/IL-13 blockade is needed. Enhanced awareness and further studies are required to better define predictive markers, pathophysiological mechanisms, and management strategies.

Keywords: dupilumab, eosinophilic pleural effusion, hypereosinophilia, biologics, asthma, CRSwNP, adverse events

Introduction

Dupilumab-associated hypereosinophilic adverse events with organ involvement have increasingly been reported in the last years, raising important therapeutic challenges in the treatment of type 2 (T2) inflammation-driven diseases.[1,2]

The advent of targeted biologic therapies has revolutionized the management of complex eosinophilic diseases.[3] Monoclonal antibodies primarily target interleukins (IL) such as IL-4, IL-5, or IL-13, and more upstream alarmins such as thymic stromal lymphopoietin (TSLP) or IL-33.[4]

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Dupilumab, a fully human monoclonal antibody, targets the alpha subunit of the IL-4 receptor, inhibiting both IL-4 and IL-13 signaling, thus preventing eosinophil transmigration from vascular circulation into tissues.[1,5] After being first approved for moderate-to-severe atopic dermatitis (AD), its indication has been widened ever since for the treatment of moderate-to-severe uncontrolled asthma, moderate-to-severe prurigo nodularis, eosinophilic esophagitis (EoE) not sufficiently responsive to proton pump inhibitor, chronic rhinosinusitis with nasal polyps (CRSwNP) not sufficiently controlled with intranasal steroids or surgery, and most recently, eosinophilic chronic obstructive pulmonary disease (COPD).[2,6]

An increase in the blood eosinophil count (BEC) is a well-known adverse event of dupilumab, that was commonly reported in pivotal Phase 3 randomized controlled trials (RCTs) as well as in real-world studies with a prevalence of up to 15%.[7–16] Dupilumab-induced hypereosinophilia is generally considered benign and self-limiting. However, small subset of patients may develop hypereosinophilia-associated adverse events that have been almost exclusively documented post-marketing in case reports.[2,7,8]

These observations highlight the importance of determining whether such organ manifestations are causally related to dupilumab therapy or represent manifestations of the underlying T2 inflammation-driven disease. A careful analysis and precise causality assessment are critical, as misconceptions can affect confidence and adherence to therapy.

This study aimed to comprehensively assess the safety profile of dupilumab with respect to hypereosinophilic adverse events and to evaluate the level of certainty of causal association. We describe a novel case of eosinophilic pleural effusion (EPE) following dupilumab therapy and expand current knowledge by characterizing the spectrum of organ manifestations associated to dupilumab-induced hypereosinophilia. Furthermore, we present a narrative literature review integrating data from the WHO global pharmacovigilance database to explore potential underlying mechanisms and assess the current body of evidence.

Materials and Methods

Literature Review and Descriptive Study of Published Case Reports

A narrative literature search was conducted using MEDLINE, Google Scholar, and Cochrane Central Register of Controlled Trials databases from inception to September 6, 2025. To ensure a comprehensive overview, we included all types of publications, comprising editorials, letters, case reports, and conference abstracts. The search was restricted to studies involving adult human participants, with no limitations on language. Articles not published in English, French or German were translated using DeepL Translator (DeepL SE, Cologne, Germany). Our objective was to identify cases of organ manifestations associated with dupilumab-induced hypereosinophilia. We conducted a literature search using the terms "dupilumab", "hypereosinophilia", "eosinophilic granulomatosis with polyangiitis", "hypereosinophilic syndrome", "eosinophilic pneumonia", and "eosinophilic pleural effusion", including both free-text terms and relevant MeSH terms, applied to titles, abstracts, and keywords. Additionally, reference lists of the included articles were screened to identify further relevant reports. Two reviewers (P.S. and V.A.B.) independently assessed the eligibility of articles retrieved from each database, discrepancies were resolved by consensus. Data were extracted and recorded in a predefined Excel table (Microsoft Corp, Redmond, WA). The literature search was also used to identify relevant publications for the discussion section. The quality and structure of the narrative review were guided by the Scale for the Assessment of Narrative Review Articles (SANRA).[17]

Institutional approval was not required for this publication. Written informed consent was obtained from the patient for the publication of their case details.

Disproportionality Data Analysis

Disproportionality analysis of individual case safety reports (ICSRs) was conducted using VigiBase (https://who-umc.org/vigibase/), the World Health Organization (WHO) global pharmacovigilance database, as the primary data source. VigiBase is the global database of the WHO Programme of International Drug Monitoring (PIDM), maintained by the Uppsala Monitoring Centre (UMC).[18] The database contains millions of ICSRs of suspected adverse drug reactions submitted by national pharmacovigilance centers from over 180 member countries of the WHO PIDM.

Relevant ICSRs were retrieved from VigiBase applying the active ingredient *dupilumab* in combination with the following Medical Dictionary for Regulatory Activities preferred terms (MedDRA - PT): *eosinophilia, hypereosinophilic syndrome, eosinophilic pneumonia, chronic eosinophilic pneumonia, eosinophilic bronchitis, eosinophilic pleural effusion, pleural effusion, eosinophilic granulomatosis with polyangiitis, erythema nodosum, urticaria, eosinophilic gastritis, eosinophilic cellulitis, eosinophilic myocarditis*, and *ischemic stroke.*

Disproportionality was quantified using the information component (IC), a statistical measure specifically developed and validated to detect disproportionately reported drug-events relative to the expected probability. As the IC is more conservative than the reporting odds ratio, we prioritized IC to limit false-positive signal detection and improve the robustness of our findings. IC is calculated as the log2 of the ratio of observed to expected reporting for a drug–event pair, with Bayesian shrinkage used to stabilize estimates for rare events.[18,19] A positive IC value reflects a reporting frequency above the expected background level based on all available data in the database, with higher IC value signifying a stronger disproportionality for the specific drug-event combination. It is important to note that the IC reflects a quantitative measure of disproportionality and does not imply a causal relationship between the drug and the adverse reaction.

For signal detection, the lower limit of the 95% confidence intervals (CIs) of IC (IC_{025}) was used, as recommended and provided by the UMC.[18,20] An $IC_{025} > 0$ was considered as a statistically significant disproportionality, with values from 0 to +1.5 indicating a weak potential drug-event association and values >+1.6 indicating a strong potential association.

The total number of globally reported ICSRs and the corresponding IC_{025} values were retrieved from VigiBase on the 15th of August 2025. Descriptive statistics were applied to analyze adverse event reports related to dupilumab. The quality and structure were guided by the international guidelines for *Reporting of A Disproportionality analysis for Drug Safety Signal Detection using individual case safety reports in Pharmacovigilance* (READUS-PV).

Results

Case Presentation

A 64-year-old female Caucasian patient was diagnosed with asthma in 2012. In late 2018, asthma control deteriorated by experiencing recurring oral corticosteroid (OCS) dependent exacerbations. Following development of CRSwNP and reactions to aspirin including nasal congestion and bronchoconstriction, aspirin-exacerbated respiratory disease (AERD) was diagnosed. Independently, a chronic spontaneous urticaria was successfully treated with omalizumab. However, this treatment had no apparent effect on the nasal and respiratory symptoms and asthma exacerbation rate.

Laboratory results consistently showed mild eosinophilia (Figure 1) and total immunoglobulin E (total IgE) and fraction of exhaled nitric oxide (FeNO) levels remained low. Initial pulmonary function tests revealed an obstructive ventilatory impairment without bronchodilator reversibility, neither on initial testing nor on follow-up spirometry (Figure 1).

Maximal topical intranasal corticosteroid therapy and a polypectomy in summer 2019 did not improve nasal obstruction or anosmia. After a multidisciplinary discussion, biologic treatment was switched to dupilumab (300 mg every 2 weeks) in August 2021 with a rapid and remarkable improvement of nasal symptoms with nearly complete restoration of smell. Furthermore, the patient experienced asthma remission and chronic spontaneous urticaria remained under control.

However, in May 2022 the patient reported right-sided chest pain during deep inspiration. Radiological evaluation revealed a homogenous pleural effusion. The symptoms recurred intermittently, significantly affecting the patient's daily activities. A thoracentesis was performed in December 2022, revealing a marked increase in eosinophils in the pleural fluid (8%) associated to a serum eosinophilia of 2520 cells/µL (reference range: < 500 cells/µL, Figure 1). Allergic bronchopulmonary aspergillosis, antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis and helminthic infestation were excluded. While a short course of OCS (Prednisone taper: 40 mg/day x5 days → 20 mg/day ×5 days → 10 mg/day ×5 days → 5 mg/day ×5 days) provided relief, EPE reoccurred upon OCS discontinuation.

After discontinuation of dupilumab, EPE resolved and asthma and CRSwNP remained controlled on medium dose inhaled corticosteroids and topic nasal therapy. Consequently, EPE was deemed an adverse event of dupilumab treatment. Six months later, both upper and lower airways diseases deteriorated, asthma exacerbations occurred, and pulmonary function worsened. Consequently, an anti-IL-5 therapy with mepolizumab was initiated. Thereafter, complete remission was achieved for both asthma and CRSwNP. Pleural effusion did not reoccur by the end of the observation period.

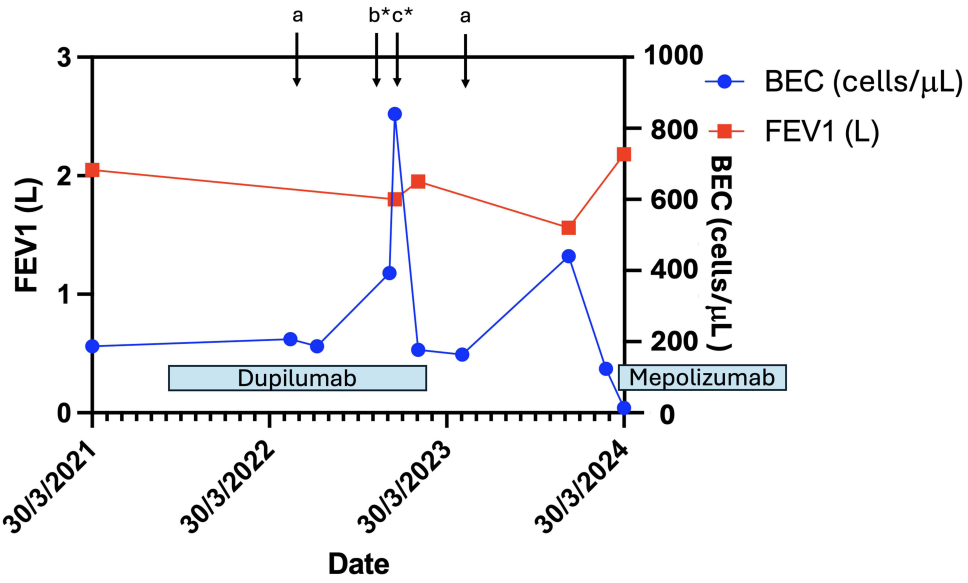

Figure 1 Evolution of BEC and FEV1 over time. [a]Absence of pleural effusion, [b]Moderate pleural effusion, [c]Large pleural effusion and moment of thoracentesis, *OCS treatment.
Abbreviations: BEC, blood eosinophilic count; FEV1, forced expiratory volume in 1 second.

Description of Published Case Reports

2405 titles were screened, and 41 reports describing 51 patients with eosinophilic adverse organ manifestations due to dupilumab were identified.[21–62] Characteristics of all reported cases, including our case (n=52), are summarized in Table 1. Indications for dupilumab administration included severe asthma (n=45; 86%), chronic rhinosinusitis with or without nasal polyps (n= 5; 67%), AD (n=6; 11%), eosinophilic otitis media (n 4; 7%), bullous pemphigoid (n 1; 2%), and eosinophilic gastrointestinal disease (n=1; 2%). A single indication was present in 37% (n=19; asthma: n = 12; chronic rhinosinusitis: n=5; AD: n=2), while in the other cases (n=33; 63%) multiple indications for dupilumab administration were reported.

Dupilumab dosing was reported in 17 cases (32%): 14 patients (82%) received 300 mg biweekly, two (12%) received 200 mg biweekly, and one (6%) received a single 600 mg dose. The median time to onset of symptoms (n=47; 90%) after the first dupilumab administration was 10.5 weeks (range 0 to 204 weeks), with 29 cases (61%) presenting a latency of less than 3 months. Latency time was not reported for seven cases.[21,22,49,62]

The following adverse events were reported, with multiple adverse events present in 8 cases (15%): eosinophilic pneumonia (EP, n=21; 40%), EGPA (n=16; 31%), HES (n=6; 12%), skin manifestations (n=5; 10%), EPE (n=3; 6%), of which one occurred within the context of EGPA,[60] eosinophilic myocarditis (n = 3; 6%), of which two occurred within the context of HES,[40,53] ischemic stroke (n=3; 6%), of which one occurred within the context of EGPA, one in the context of a not otherwise specified eosinophilic vasculitis, and one shortly after discontinuation of dupilumab and initiation of treatment for eosinophilic pneumonia, eosinophilic bronchitis (n=1; 2%), eosinophilic gastritis (n=1; 2%) and eosinophilic cellulitis (n=1; 2%).[22,29]

Median absolute BEC (n=43, 82%) at onset of adverse event was 6280 cells/µL (range 700–42800 cells/µL), and relative BEC 30.6% (n=15, 29%; range 5.3–70.7%). Severe hypereosinophilia > 3000 cells/µL was reported in 29 (67%), and mild elevated BEC of < 1500 cells/µL in 7 cases (16%). In patients with an EP (n=21; 40%), bronchoalveolar lavage (BAL) was performed in 14 (66%) patients with an EP, with a median BAL eosinophil count of 40% (range 6–76%).

Dupilumab was discontinued in 94% (n=49) and continued in 6% (n=3) of the cases. In two cases an anti-IL-5 biologic was successfully added to the continued dupilumab treatment.[28,60] In the majority of the patients, systemic steroids were introduced (n=47; 90%). Seven out of 16 patients (44%) with EGPA received other immunosuppressive agents in addition to steroids, including cyclophosphamide (n=3; 19%), rituximab (n=2; 12.5%), azathioprine (n=1; 6%), and colchicine (n=1; 6%).

Table 1 Patient Characteristics

Case	Sex	Age	Total Treatment Duration Prior to Adverse Event	Dupilumab Dosage	BEC at Onset		Indication and Comorbidities	Adverse Event	Dis-Continuation of Dupilumab	Treatment of Adverse Event
		Years	Weeks	mg	Cells/μL	%				
Index	F	64	36	300	2500	26.7	Asthma, CRSwNP	EPE	Yes	CS, mepo
Menzella, 2019[23]	M	56	20	300	2100	26.2	Asthma, CRSwNP	EP	Yes	CS
Devaraj, 2020[24]	M	58	6	NR	3200	NR	Asthma	EP	Yes	CS
Iwamuro, 2020[25]	M	77	12	NR	400	5.3	Asthma, CRS	Eosinophilic gastritis	Yes	CS
Eger, 2021[22]	F	59	NR	NR	5100	NR	Asthma, CRS	EP, EV	Yes	CS, anticoagulation, benra
	F	63	12	NR	3900	NR	Asthma	EGPA	Yes	CS, mepo
Adunse, 2021[26]	F	55	6	NR	NR	17	Asthma, BP, AD	EP	Yes	CS
Briegel, 2021[27]	M	50	2	300	3900	NR	Asthma, CRSwNP	EP	Yes	CS, benra
Descamps, 2021[28]	F	61	32	300	11500	NR	Asthma, CRSwNP	EV (skin)	No	Benra
Lommatzsch 2021[29]	F	66	6	300	11,000	41.9	Asthma	EV (skin)	Yes	CS
	M	49	6	200	10,500	50.2	Asthma, CRSwNP	EPE	Yes	CS, benra
Murag, 2021[30]	M	41	12	NR	1300	NR	Asthma, CRSwNP, AD	EGPA	Yes	CS, mepo
Tanaka, 2022[31]	M	in 50'	20	NR	17400	NR	Asthma, CRSwNP	EGPA	NR	CS
Nishida, 2022[32]	F	72	28	300	4800	28	CRSwNP	EP	Yes	CS
Nishiyama, 2022[33]	F	37	20	NR	9000	NR	Asthma, CRS	EP	NR	CS
	F	40	12	NR	5200	NR	Asthma, CRS	EP	NR	CS
Gharaibeh, 2022[34]	F	66	4	NR	11200	35	Asthma	EP	NR	CS
Yamazaki, 2022[35]	F	77	24	300	800	NR	Asthma, CRSwNP, EP	EGPA	NR	CS
Kurihara, 2022[36]	F	55	5	NR	NR	30,1	Asthma, EOM, CRS	EP	NR	CS, benra
	M	59	11	NR	NR	26,5	CRSwNP	EP	NR	CS
Frohlich, 2022[37]	F	51	16	NR	700	NR	Asthma	EP	NR	CS
	F	58	14	NR	24000	NR	Asthma, CRSwNP	EP	NR	CS

(*Continued*)

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Table 1 (Continued).

Case	Sex	Age	Total Treatment Duration Prior to Adverse Event	Dupilumab Dosage	BEC at Onset		Indication and Comorbidities	Adverse Event	Dis-Continuation of Dupilumab	Treatment of Adverse Event
Sudo, 2022[38]	F	65	10	NR	NR	NR	CRSwNP	EP	No	CS
Persaud, 2022[39]	M	58	1	NR	NR	70.7	CRS	EGPA	NR	CS, rituximab
Abulhamail, 2022[40]	F	77	12	NR	30800	NR	Asthma, CRSwNP	HES	NR	CS, mepo
Mustin, 2022[41]	F	74	8	300	2500	NR	Asthma, CRSwNP	Erythema nodosum	Yes	CS, omalizumab
von Deimling, 2023[21]	M	65	NR	NR	700	NR	Asthma	EGPA	NR	CS
	F	59	NR	NR	900	NR	CRSwNP	EGPA	NR	CS
Suzaki, 2023[42]	F	63	4	300	NR	NR	Asthma, EOM, CRS	EGPA	Yes	CS, azathioprine, mepo
Covarel, 2023[43]	M	57	20	NR	2400	NR	Asthma	EGPA	Yes	CS, CP
Hu, 2023[44]	F	64	8	NR	6300	NR	Asthma, CRSwNP	EGPA	Yes	CS, CP
Kamimura, 2023[45]	F	55	0	NR	NA	55	Asthma, CRSwNP	EGPA	Yes	CS
Kanata, 2023[46]	F	63	8	NR	7400	NR	Asthma, AD	EP	Yes	CS
Kai, 2023[47]	F	67	44	NR	1100	NR	Asthma, CRSwNP	EGPA	NR	CS, mepo
Abushanab, 2024[48]	F	24	8	300	18800	NR	Asthma, CRS	Eosinophilic cellulits	Yes	CS, benra
Ashraf, 2024[49]	F	48	3	NR	42800	NR	Asthma, CRSwNP	HES	Yes	CS
Fargeas, 2024[50]	F	36	32	NR	1000	NR	Asthma, CRSwNP, HES	EGPA	NR	CS, CP
	F	63	16	NR	14000	NR	Asthma, CRSwNP	EGPA	NR	CS, rituximab
Hamakawa, 2024[51]	F	77	4	NR	9600	NR	Asthma	EP	Yes	CS, benra
	F	50	16	NR	7600	NR	Asthma, CRS	EP	No	CS
Nadeem, 2024[52]	F	44	6	NR	13200	56	Asthma	HES	Yes	CS, benra
Saffari, 2024[53]	F	25	8	NR	28000	NR	Asthma	HES	Yes	CS
Li, 2024[54]	M	43	204	300	2600	NR	AD	HES	Yes	No treatment
Gawlewicz-Mroczka, 2024[55]	F	52	8	200	4900	54.3	Asthma	EP, erythema nodosum	Yes	CS

Nakashima, 2024[56]	M	54	24	NR	NR	30.6	Asthma, EOM, CRS	EP	NR	CS
Zhou, 2024[57]	M	71	0	600	1600	NR	AD	EP	NR	CS
Naidu, 2025[58]	M	48	1	300	9400	NR	Asthma, CRSwNP	Eosinophilic myocarditis	Yes	CS, mepo
Kaburaki, 2025[59]	F	48	2	NR	11900	NR	Asthma, CRSwNP	EGPA	Yes	CS, mepo, IVIG
Ezekwe, 2025[60]	F	27	6	NR	13500	NR	Asthma, CRSwNP	EGPA	Yes	CS, colchicine
	M	29	16	300	26800	NR	Asthma, CRS	EP, eosinophilic neuropathy	No	CS, mepo
Goundry, 2025[62]	M	33	NR	NR	28900	NR	Asthma, AD	HES with colitis	Yes	CS
Kikuoka, 2025[61]	F	23	2	300	2400	NR	Asthma, CRSwNP	EP	Yes	CS

Abbreviations: AD, atopic dermatitis; benra, benralizumab; BP, bullous pemphigoid; CP, cyclophosphamide; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyposis; CS, corticosteroids; EGPA, eosinophilic granulomatosis with polyangiitis; EOM, eosinophilic otitis media; EP, eosinophilic pneumonia; EPE, eosinophilic pleural effusion; EV, eosinophilic vasculitis; F, female; HES, hypereosinophilic syndrome; IVIG, intravenous immunoglobulin; M, male; mepo, mepolizumab; NR, not reported.

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In 16 patients, dupilumab was switched to another biologic, including mepolizumab (n=8; 50%), benralizumab (n=7; 44%) and omalizumab (n=1; 6%).

Six patients were reexposed to dupilumab. In two patients, erythema nodosum relapsed 6 weeks and 1 week after resuming dupilumab, respectively.[41,55] In one patient, HES reoccurred after 16 weeks, but was self-limiting and dupilumab was continued.[54] In three patients with EP, no relapse was observed at 10 months of reexposure.[38,57,61]

All patients for which the outcome was reported (n=41; 79%) showed a full recovery or significant clinical improvement by the end of the observation period. No fatalities were reported.

Disproportionality Data Analysis

A total of 338'612 adverse events associated to dupilumab have been reported to VigiBase. Since 2018, the reporting rates were continuously increasing, with a peak observed in 2024 (82'735 reports, 24%).

A strong positive association was observed for dupilumab and EGPA (195 reports; IC_{025} +3.4), chronic eosinophilic pneumonia (24 reports; IC_{025} +3.2), HES (31 reports, IC_{025} +2.8), EP (162 reports; IC_{025} +2.6), EPE (14 reports; IC_{025} +2.2), and eosinophilia (858 reports; IC_{025} +1.7). A weak positive association was observed for dupilumab and erythema nodosum (including *erythema nodosum-like lesion*, 149 reports; IC_{025} +1.0), and eosinophilic myocarditis (11 reports; IC_{025} +0.6) (Figure 2).

The remaining declared eosinophilic adverse events were not disproportionately reported than the expected probability, resulting in a negative association for dupilumab and pleural effusion (82 reports; $IC_{025\ -2}$.7), eosinophilic cellulitis (including Wells syndrome, 4 reports, IC_{025} −0.9), urticaria (4176 reports; IC_{025} −1.0), eosinophilic bronchitis (2 reports, IC_{025} −1.0), eosinophilic gastritis (1 report, IC_{025} −2.7) and ischemic stroke (21 reports, IC_{025} −3.5).

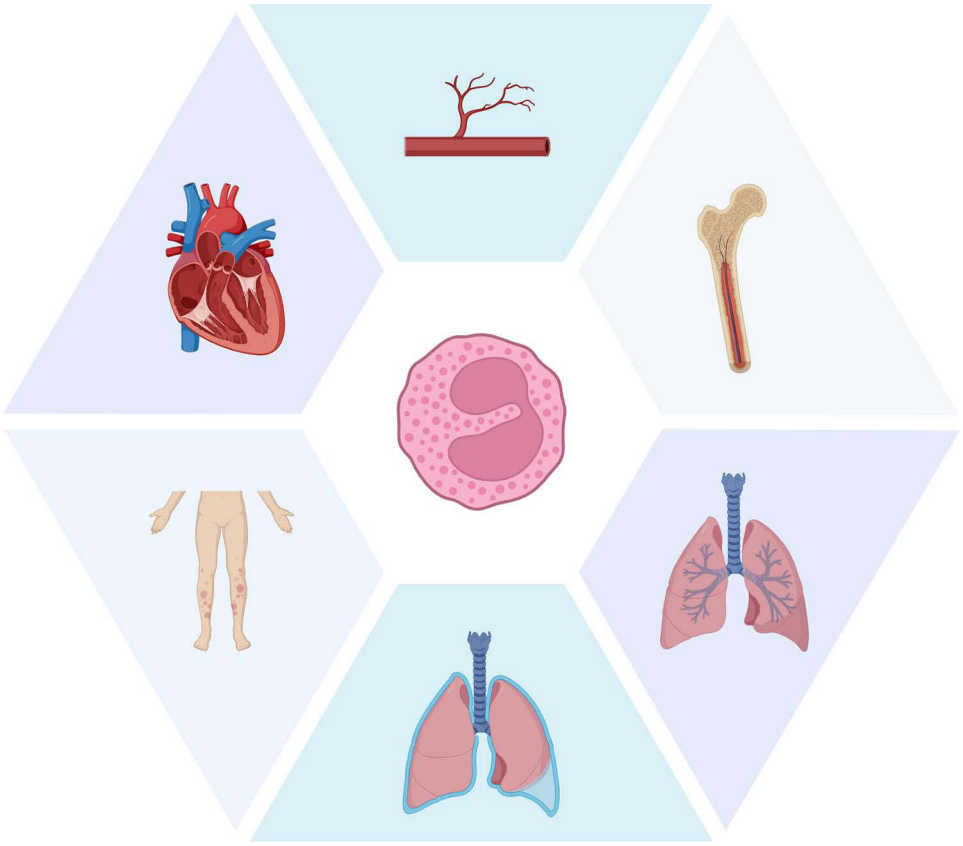

Figure 2 Eosinophilic adverse events associated with dupilumab therapy in WHO Global Pharmacovigilance Database, VigiBase. From the top center in a clockwise direction: eosinophilic granulomatosis with polyangiitis (195 reports; IC025+3.4), hypereosinophilic syndrome (31 reports, IC025+2.8), eosinophilic pneumonia (162 reports; IC025+2.6), eosinophilic pleural effusion (14 reports; IC025+2.2), erythema nodosum (149 reports; IC025+1.0), eosinophilic myocarditis (11 reports; IC025+0.6).

Discussion

Case discussion

We present the case of a patient with AERD with severe asthma and CRSwNP, who developed a right-sided EPE 9 months after initiating dupilumab treatment. While short courses of OCS provided only transient relief, a complete resolution could be achieved only after discontinuation of dupilumab. Other causes of EPE such as malignancies, infections, drug reactions, hemothorax, pneumothorax, chest trauma or repeated thoracentesis were excluded.[63,64]

EPEs result from cytokine-driven eosinophil proliferation, followed by migration into the lungs and accumulation in the pleural space, where activated eosinophils release pro-inflammatory mediators that drive effusion development. Although, the criteria for EPE (arbitrary cutoff set at 10% eosinophils in the pleural effusion) were not fully met, the clinical context justified its classification as EPE.[65–67] Several factors may explain why the formal cutoff for EPE was not met in our patient. First, prior OCS treatments could lead to a long-term reduction of blood eosinophils and hence, tissue and pleural effusion eosinophils. Second, delayed increase of tissue eosinophils after OCS discontinuation have been described previously in asthma patients.[11] Third, the reduced transmigration of eosinophils into tissues can be attributed to the pharmacological effects of dupilumab, which likely contributes to the lower eosinophil count observed in the pleural effusion.[68,69]

A consistent temporal pattern, a plausible biological mechanism (as discussed below), and a positive safety signal linking dupilumab to EPE (14 reports; IC_{025} +2.2) are suggestive of a causal association. Nevertheless, underreporting is likely, as small effusions may be clinically not relevant or missed without follow-up imaging, and diagnostic pleural puncture with cytological evaluation is not consistently conducted when a pleural effusion is present.

Dupilumab Associated Hypereosinophilia

Clinical trials evaluating the long-term safety and efficacy of dupilumab across various T2-diseases have reported mostly transient increases in BEC, with return to baseline within a few months.[16,61,70–74]

Several mechanisms for dupilumab-induced eosinophilia have been proposed (Figure 3), suggesting a complex interplay between cytokine blockade, eosinophil trafficking, and tissue infiltration resulting in localized eosinophilic inflammation despite overall clinical improvement of T2-mediated conditions.[1,75] Moreover, disease-specific immune pathways were discussed as potential underlying causes of eosinophilia.[6]

First, IL-4 regulates the expression of chemotactic molecules on endothelial cells, such as vascular cell adhesion molecule-1 (VCAM-1), which facilitates eosinophil adhesion to endothelial cells. Disease specific expression of VCAM-1 may explain the absence of blood eosinophilia in COPD or EoE compared to other T2-inflammatory diseases.[6] IL-13 promotes the production of eotaxins, key chemokines that direct eosinophil migration from the bloodstream to peripheral organs.[76] The dual inhibition of IL-4/IL-13 signaling by dupilumab leads to eosinophil retention in the vascular circulation, considered to be the most likely explanation for dupilumab-induced eosinophilia.[6,68,69]

Second, blockade of IL-4/IL-13 signaling does indirectly increase IL-5 production, which continues to stimulate eosinophil production in the bone marrow.[6,77]

Third, many patients receive OCS at initiation of dupilumab treatment. OCS are highly effective at suppressing blood eosinophils. Once dupilumab is introduced and OCS are tapered, a subsequent increase in eosinophil counts may be observed.[78,79]

Eosinophils express surface receptors for various cytokines, including IL-4 and IL-13, which play key roles in promoting and sustaining eosinophilic inflammation in T2-mediated diseases. Therefore, blocking these two interleukins can reduce in the long-term both the production and activity of eosinophils. This effect may help counterbalance the rise in BEC seen with dupilumab and could explain the mostly transient nature of dupilumab-induced hypereosinophilia.[7]

Dupilumab-Associated Adverse Events

Common adverse events associated with dupilumab include local injection site reactions, ophthalmic adverse events (eg conjunctivitis, keratitis, blepharitis, dry eyes), arthritis and arthralgia.[80]

Dupilumab-induced hypereosinophilia is usually benign, and eosinophilic adverse events with organ involvement are rare; however, both can pose significant challenges for clinical management. Patients with higher baseline BEC are at

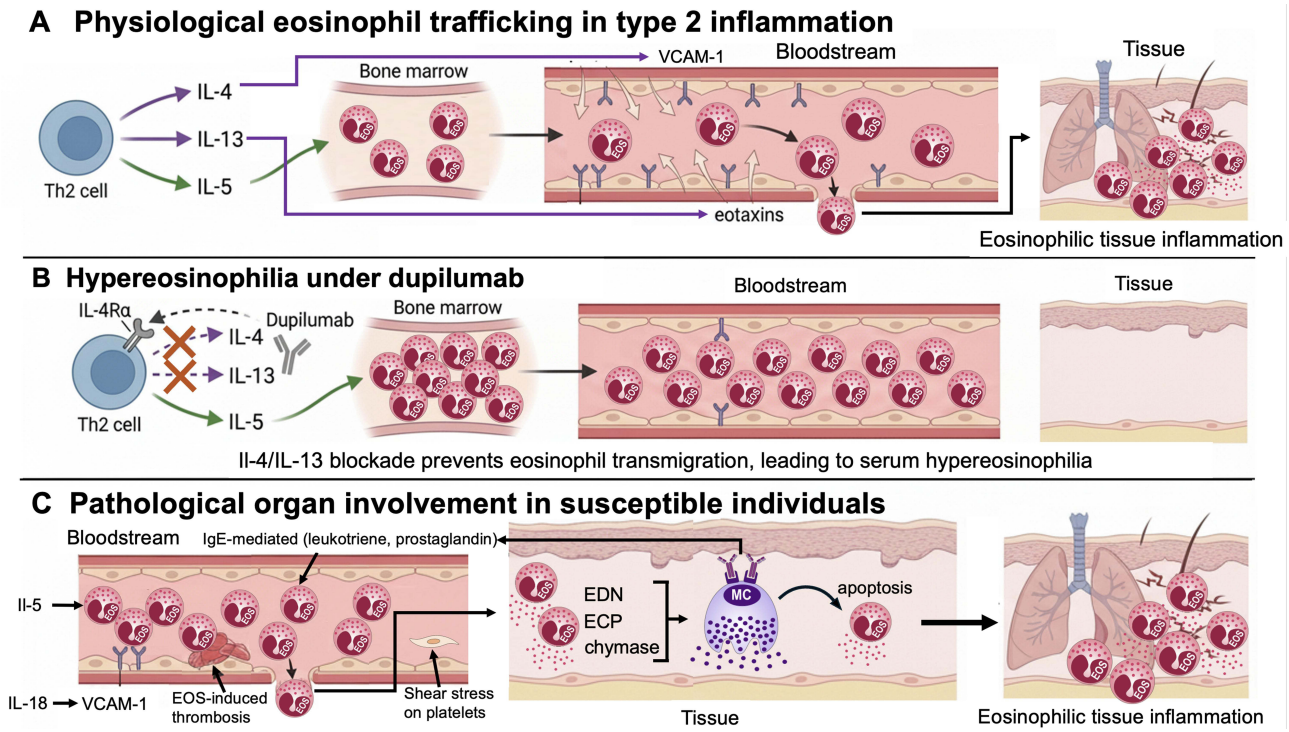

Figure 3 Proposed mechanisms of dupilumab-associated hypereosinophilia and hypereosinophilic organ manifestations. (**A**) Physiological eosinophil trafficking in type 2 inflammation. (**B**) Hypereosinophilia under dupilumab. (**C**) Pathological organ involvement in susceptible individuals.
Abbreviations: EOS, eosinophil; ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; IgE, immunoglobulin EIL, interleukin; MC, mast cell; VCAM-1, vascular cell adhesion molecule 1.

increased risk of developing hypereosinophilia compared to those with lower baseline levels.[81] Rampi et al proposed that BEC levels at two months may help predict persistent hypereosinophilia, suggesting that early BEC trends could have clinical relevance[82] Other risk factors associated with dupilumab-induced hypereosinophilia may include multiple T2-associated comorbidities, FeNO ≥ 60 ppb and sensitization to food allergens.[74]

Furthermore, some cases ultimately consistent with EGPA may have been initially misdiagnosed as eosinophilic asthma, with the correct diagnosis only unmasked after dupilumab initiation and subsequent OCS tapering.[83] However, the significant positive safety signal for dupilumab and EGPA (IC_{025} +3.4) suggests the possibility of an underlying mechanism that may contribute to disease evolution toward EGPA.

Dupilumab-Induced Hypereosinophilic Organ Manifestations

Since 2019, a steadily increasing number of cases of eosinophilic adverse events with organ involvement in temporal association with the initiation of dupilumab treatment have been published.

BEC levels do not correlate with the occurrence and severity of eosinophilic organ manifestations and the exact relationship between dupilumab-induced hypereosinophilia and eosinophilic tissue infiltration remains incompletely understood.[84] Nevertheless, hypereosinophilia per se can trigger inflammatory cascades, induce endothelial damage and promote cellular transmigration through a variety of distinct mechanisms (Figure 3).

Circulating eosinophils may be activated either directly through IgE-mediated mechanisms or indirectly through mast cell-derived mediators, such as IL-5, leukotrienes, or prostaglandin D2, which migrated back into the vessels following local mast cell activation.[85] Even in the absence of any exogenous eosinophil activation, physical contact of eosinophils with surface-bound platelets under conditions of low shear stress can trigger a cascade of immunomodulators responses. This may lead to a firm, shear-resistant adhesion and subsequent secondary cell transmigration.[86] Furthermore, it may also result in eosinophil-induced thrombosis, resulting in localized ischemia and further facilitation of eosinophil recruitment and tissue migration.[85,87] Additionally, activated eosinophils contribute to oxidative stress and consequent

tissue damage through cytotoxic granule proteins such as eosinophil cationic protein (ECP) or serum eosinophil-derived neurotoxin (EDN).[85,88] Once activated within the vessels, eosinophils then maintain and amplify T2 immune responses, thereby establishing a self-perpetuating inflammatory loop.

Furthermore, epithelial-derived cytokines such as TSLP, IL-25 or IL-33, released during epithelial barrier disruption, can activate type 2 innate lymphoid cells (ILC2), which in turn produce IL-13. This increases vascular permeability and enhances eosinophil migration into tissues, which can even be the case in the context of IL-4Rα blockade.[83] Once eosinophils infiltrate the tissue, degranulation leads to exacerbation of inflammation and direct tissue damage. Simultaneously, mast cell-derived chymase may inhibit eosinophil apoptosis, thereby prolonging their pro-inflammatory activity.[89]

In certain types of T2 inflammation, the IL-4 and IL-13-independent cytokine IL-18 is overexpressed and has been shown to promote eosinophil differentiation and migration through upregulation of VCAM-1 on endothelial surface. Elevated IL-18 levels in specific patient populations, such as those with asthma or CRSwNP, may increase the risk of eosinophilic organ involvement. In contrast, conditions like COPD or EoE have been associated with lower rates of eosinophilia during dupilumab treatment probably due to lower IL-18 expression.[6] Our review found also hypereosinophilic organ manifestations mainly in patients with asthma and CRSwNP. In consequence, this mechanism may explain the predominance of pulmonary and vascular adverse events such as EP, EPE, and EGPA.

Furthermore, the temporal proximity in most reported cases, associated with the plausible pharmacological mechanisms, supports the hypothesis of a potential causal relationship between dupilumab and eosinophilic adverse events with organ involvement. With increasing use of dupilumab, coincidental cases of eosinophilic adverse events may be observed more frequently. Current global pharmacovigilance data support an association between the use of dupilumab and EGPA, EP, EPE and HES. While these safety signals from the global pharmacovigilance database are indicative for an association between the use of dupilumab and those eosinophilic adverse events with organ involvement, they do not proof a causal relationship and need to be considered for further investigation.

Management of Dupilumab-Induced Hypereosinophilia

Given the unpredictable nature of eosinophilic responses to dupilumab, clinicians must carefully balance therapy continuation with the risk of adverse events. There are no formal clinical guidelines for managing dupilumab-induced hypereosinophilia and current practice is guided by expert opinions.[10] In cases of BEC < 1500 cells/μL without organ manifestations, a "watchful waiting" approach may be appropriate. However, persistent BEC > 1500 cells/μL is generally considered a risk for potential organ involvement, warranting a closer monitoring and further investigations, including functional assessments and imaging at regular intervals. When the BEC exceeds 5000 cells/μL or is repeatedly > 3000 cells/μL, referral for a specialized hematologist assessment is recommended.[1]

Like dupilumab-associated eosinophilic organ manifestations seem reversible, and no fatalities have been reported, the withdrawal of dupilumab therapy represents the cornerstone in their management. In most cases oral or intravenous corticosteroids were introduced. Some case reports described the resumption of dupilumab and introduction of an anti-IL-5 monoclonal antibody as an add-on in order to suppress the eosinophilic activity and to avoid the interruption of an effective therapy, especially when no suitable treatment alternatives were available.[22,27–29,81]

Limitations

The study is limited by its reliance on case reports and pharmacovigilance data, which are subject to underreporting and reporting bias. A positive association indicates a more frequent reporting to the database than expected but does not permit to conclude a causal link. Prospective studies are needed to clarify the clinical significance of dupilumab-associated eosinophilic adverse events with organ involvement.

Conclusion

In conclusion, this review illustrates the importance of vigilant monitoring for eosinophil-associated adverse events during dupilumab therapy, even in the context of overall clinical improvement, and highlights the complex and not fully understood interplay between cytokine blockade and eosinophil trafficking. It emphasizes the need for greater awareness

and further research into the pathophysiological mechanisms, risk factors, and optimal management strategies for dupilumab-induced hypereosinophilia to guide clinical decision-making in complex cases.

Clinical Trial Registration/Consent for Publication

Written informed consent was obtained from the patient for their case details to be published.

Abbreviations

AERD, Aspirin-exacerbated respiratory disease; ANCA, antineutrophilic cytoplasmic antibody; BAL, bronchoalveolar lavage; BEC, blood eosinophil count; CRSwNP, chronic rhinosinusitis with nasal polyps; COPD, eosinophilic chronic obstructive pulmonary disease; EGPA, eosinophilic granulomatosis with polyangiitis; EoE, eosinophilic esophagitis; EP, eosinophilic pneumonia; EPE, eosinophilic pleural effusion; FeNO, fraction of exhaled nitric oxide; HES, hypereosinophilic syndrome; IC, information component; ICS, inhaled corticosteroids; Total IgE, total immunoglobulin E; IL, interleukin; ILC2, type 2 innate lymphoid cells; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; OCS, oral corticosteroids; RCT, Randomized controlled trial; SANRA, Scale for the Assessment of Narrative Review Articles; T2, Type 2 (Inflammation); TSLP, thymic stromal lymphopoietin; VCAM-1, Vascular cell adhesion molecule 1; WHO, World health organization.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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