Dupilumab-associated hypereosinophilia in severe asthma

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To the Editor:

Dupilumab is a monoclonal antibody directed at the shared α-subunit of interleukin-4 and -13 receptors, and is subsidised in Australia for severe uncontrolled asthma [1–4]. Dupilumab inhibits eosinophil migration into tissues but does not inhibit eosinophil production or release from bone marrow, resulting in a transient increase in circulating eosinophils [1]. There have been reports of symptomatic dupilumab-associated hypereosinophilia [3, 5].

In phase III trials, rates of dupilumab-associated hypereosinophilia $\geqslant 1.5\times10^9$ cells per L in airways disease differed by treatment indication [2, 3, 5, 6]. The highest rate occurred in oral corticosteroid (OCS)-dependent severe asthma (35.9%), followed by moderate-to-severe asthma (14.7%) and chronic rhinosinusitis with nasal polyposis (CRSwNP) (7.2%) [2, 3, 5, 6]. In the OCS-dependent asthma trial, hypereosinophilia was always asymptomatic [2]. In moderate-to-severe asthma, four (0.3%) out of 1264 patients had symptomatic hypereosinophilia [3]. In CRSwNP, three (0.7%) out of 438 patients had symptomatic hypereosinophilia, two with eosinophilic granulomatosis with polyangiitis (EGPA) [5]. *Post hoc* analysis of all randomised controlled and open-label extension studies of dupilumab found elevated baseline eosinophils ($>0.5\times10^9$ per L) were associated with a higher likelihood of hypereosinophilia during treatment [6].

Given the above, we monitored consecutive adult patients commencing dupilumab for severe asthma from November 2020 to November 2022 at Alfred Health in Melbourne, Australia. We measured serum eosinophils at baseline, and 4 and 16 weeks, with time points chosen based on trends in clinical trials [6]. We defined eosinophilia as $\geqslant 0.5\times10^9$ cells per L and hypereosinophilia as $\geqslant 1.5\times10^9$ cell per L [7]. We contacted patients at weeks 4 and 16 to screen for new-onset symptoms that have previously been reported as dupliumab-related adverse reactions (fever, myalgia, arthralgia, worsening asthma, rash, chest pain or neurological symptoms) [2, 3, 5, 8, 9]. Ethics approval was obtained to report these data (Human Research Ethics Committee 492/23) and need for informed consent was waived.

Over 2 years, 69 patients commencing on dupilumab for severe asthma underwent monitoring. 64 met Australian Pharmaceutical Benefits Scheme (PBS) subsidy criteria. Five patients commenced dupilumab through compassionate access; four prior to PBS subsidy in April 2021 and one with controlled severe asthma but uncontrolled CRSwNP. Mean age was 53 years and 44% were male (table 1). Mean±SD prebronchodilator FEV_1 was 71±21% predicted (mean±SD). 13 (18%) patients were on maintenance OCS.

In 16 (23%) out of 69 patients, dupilumab was the first asthma biologic. The others were switched from omalizumab (n=15), mepolizumab (n=24) or benralizumab (n=14). One patient had an adverse reaction to the previous biologic.

At baseline, the mean±SD serum eosinophil count was $0.37\pm0.36\times10^9$ per L. 23 (33%) out of 69 patients had eosinophilia between 0.5 and 1.5×10^9 cells per L and one had hypereosinophilia (1.7×10^9 cells per L). While continuing dupilumab, this patient's eosinophils remained stable at (0.7×10^9 per L at 4 weeks and 1.2×10^9 per L at 16 weeks).

At week 4, 56 (81.1%) out of 69 patients responded to phone calls and 44 (63.8%) out of 69 had eosinophils measured ($0.48\pm0.77\times10^9$ per L). Eosinophilia was detected in 15 (22%) out of 69 patients. Of these, five also reported arthralgia, conjunctivitis, headache or rash, but were able to continue dupilumab.

Shareable abstract (@ERSpublications)
Dupilumab has been associated with adverse reactions including symptomatic hypereosinophilia. This study reports the incidence of dupilumab-related eosinophilia and adverse reactions in severe asthma patients at an Australian tertiary centre. https://bit.ly/3JgZ5Ya

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TABLE 1 Overview of patient cohort and details of patients with dupilumab-associated hypereosinophilia

Patient	Age, years	Sex	Maintenance OCS	$FEV_1^{\#}$, % predicted	Previous biologic	CRS	Baseline EoS, $\times10^9$ per L	Week 4		Week 16		Ceased dupilumab
								EoS, $\times10^9$ per L	Symptoms	EoS, $\times10^9$ per L	Symptoms	
All (n=69)	53	44% male	13/69 (18%)	71±21	53/69 (77%)	39/69 (56%)	0.37±0.36 Eosinophilia[¶] 23/69 (33%) Hypereosinophilia[+] 1/69 (1%)	0.48±0.77 Eosinophilia[¶] 15/69 (22%) Hypereosinophilia[+] 1/69 (1%)	16/69 (23%): Arthralgia (n=6) Headache (n=3) Rash (n=3) *etc.*	0.90±1.64 Eosinophilia[¶] 12/65 (18%) Hypereosinophilia[+] 4/65 (6%)	12/65 (18%): Arthralgia (n=3) Worse asthma (n=3) Injection site reactions (n=2) *etc.*	8/69 (12%): Symptomatic hypereosinophilia[+] (n=4) Worsening asthma (n=2) Worsening CRS (n=1) Arthralgia (n=1)
Patients with dupilumab-associated hypereosinophilia												
1	52	F	N	35%	Benralizumab	Y	0.00	4.90	Alopecia	0.40	Alopecia	N
2	64	M	N	89%	Benralizumab	Y	0.50	0.12	N	2.00	N	N
3	29	F	Self-ceased	85%	Mepolizumab	N	0.60	1.20	N	9.00	Chest pain, headache	At week 16
4	69	M	N	102%	N	Y	0.80	0.12	N	2.50	N	At 6 months (arthralgia)
5	63	F	N	73%	Mepolizumab	Y	0.05	0.10	Arthralgia, lethargy, headache	5.00	Arthralgia, lethargy, headache	At week 16
6	64	M	Y	64%	Mepolizumab	N	0.30	–	–	0.00	N	At 6 months (EGPA on MRI with subendocardial fibrosis and apical thrombus, EoS 2.0×10^9 per L)

Data are presented as mean±SD unless otherwise stated. OCS: oral corticosteroids; FEV_1: forced expiratory volume in 1 s; CRS: chronic rhinosinusitis; EoS: eosinophils; –: not performed; EGPA: eosinophilic granulomatosis with polyangiitis; MRI: magnetic resonance imaging. [#]: prebronchodilator; [¶]: EoS $\geqslant0.5\times10^9$ per L; [+]: EoS $\geqslant1.5\times10^9$ per L.

In total, 16 (23%) out of 69 patients reported adverse reactions, most commonly arthralgia, headache and rash. Dupilumab was ceased in two (3%) patients due to worsening asthma. One patient developed hypereosinophilia, whose baseline eosinophils were 0.4×10^9 per L but rose to 4.9×10^9 per L by week 4, accompanied by subjective hair loss (table 1). Given previous treatment failure to benralizumab, dupilumab was continued with OCS cover, on which eosinophilia resolved to 0.4×10^9 cells per L at week 16.

At week 16, two further patients had ceased dupilumab due to worsening rhinosinusitis and arthralgia patients, without hypereosinophilia. 56 (86%) out of 65 patients on treatment responded to telephone calls and 36 (55%) out of 65 had eosinophils measured ($0.9\pm1.64\times10^9$ per L). 12 (18%) out of 65 patients reported adverse reactions, most commonly arthralgia, asthma and injection site reactions. Eosinophilia occurred in 12 (18%) out of 65 patients. Hypereosinophilia was detected in four (6%) out of 65 patients. One of these (with baseline eosinophilia of 0.5×10^9 cells per L rising to 2.0×10^9 cells per L by week 16) was asymptomatic and continued on dupilumab. Three others developed symptoms requiring dupilumab cessation.

One had known idiopathic hypereosinophilic syndrome in addition to severe asthma, with previous incomplete response to mepolizumab and baseline eosinophilia (0.6×10^9 cells per L). The patient was switched to dupilumab with OCS cover but, unfortunately, self-ceased OCS. Eosinophils rose from 1.0×10^9 per L at week 4 to 9.3×10^9 per L at week 16, associated with chest pain and headache. The patient was switched back to mepolizumab.

Another patient had baseline eosinophils of 0.8×10^9 per L, 0.1×10^9 per L at week 4 and 2.5×10^9 per L at week 16, persisting above 2.0×10^9 per L on serial testing. Dupilumab was continued until the patient developed arthralgia at 6 months, when the patient was switched to mepolizumab.

A third patient had eosinophils of 0.05×10^9 per L at baseline and 0.10×10^9 per L at week 4, rising to 5.0×10^9 per L at week 16, in association with arthralgia, headache and lethargy, when the patient was switched to benralizumab.

At 6 months, a final case of symptomatic dupilumab-associated hypereosinophilia (2.0×10^9 cells per L) was detected when the patient presented to another institution with symptoms suggesting EGPA and magnetic resonance imaging indicating cardiac involvement. Dupilumab was ceased. The patient had been on maintenance OCS throughout. Eosinophil counts at baseline and 16 weeks had been 0.3×10^9 and 0.02×10^9 per L respectively (no testing at week 4).

In this severe asthma clinical cohort, the overall rate of dupilumab-associated hypereosinophilia (six out of 69; 8.7%, 95% CI 3.2–18.9%) fell within the range reported in severe asthma clinical trials [2, 3]. Three of the six hypereosinophilic patients had baseline eosinophilia before treatment.

However, the incidence of symptomatic hypereosinophilia with clinical manifestations (four out of 69; 5.8%, 95% CI 1.6–14.8%) was higher than the corresponding 0–0.3% observed in severe asthma randomised trials [2, 3], and prompted relevant treatment cessation between 16 weeks and 6 months. Even excluding the patient with concurrent idiopathic hypereosinophilic syndrome from analysis (where hypereosinophilia may have been due to underlying disease rather than dupilumab) still yielded a rate (three out of 69; 4.3%, 95% CI 0.9–12.7%) higher than in randomised asthma trials. This may be due to patient selection. Biologic prescribing in clinical cohorts like ours is often less restrictive than occurs in clinical trials, and for patients with greater disease severity and clinical complexity, who might otherwise be excluded from studies.

In total, eight (12%) out of 69 patients ceased dupilumab during follow up. Adverse symptoms were common (16 (23%) out 69 at 4 weeks) but less frequent than in clinical trials. Most patients with symptoms did not have hypereosinophilia, and most could continue dupilumab, consistent with published literature [4–9].

Our analysis was limited by missing data within a clinical monitoring programme but the results reflect real-world dupilumab prescribing for severe asthma in the Australian health care setting and suggest the need for larger real-world studies.

Dupilumab prescribers should be alert to symptomatic hypereosinophilia during treatment for severe asthma, potentially affecting roughly one in 20 patients in clinical practice. Patients should be advised of this possibility prior to dupilumab initiation and counselled regarding the need to report relevant specific symptoms. Symptomatic patients should be assessed and have eosinophil counts serially checked. Based

on the literature [6] and our experience, asymptomatic patients with baseline eosinophilia $\geqslant 0.5\times10^9$ cells per L may also be considered for eosinophil count monitoring. Guidelines advise against initiating dupilumab in patients with current or historical hypereosinophilia [10].

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Conflict of interest: Unrelated to this study, in the past 36 months, A. Sverrild has received research grants paid to their employer from AstraZeneca, and speaker fees from AstraZeneca and Sanofi. A. Sverrild serves on advisory boards for GlaxoSmithKline and Sanofi-Regeneron with honoraria made to their institution. Unrelated to this study, J. Lee has received speaker fees from AstraZeneca, Sanofi and GSK, as well as serving on the board of the National Allergy Centre of Excellence. Unrelated to this study, in the past 36 months, C. Zubrinich has received speaker fees and grants from Novartis, Mylan, Seqirus, Inovating and Inside Practice. Unrelated to this study, E. Denton declares project grants to her institution from AstraZeneca, GlaxoSmithKline, Novartis, Sanofi, Teva and Seqirus, and speaker fees from Sanofi. Unrelated to this study, M. Hew has received grants and personal fees from GlaxoSmithKline, AstraZeneca, Sanofi, Novartis, Teva and Chiesi, all paid to his employer Alfred Health. The remaining authors have nothing to disclose.

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