

Review

Friend or Foe? Eosinophilic Granulomatosis with Polyangiitis (EGPA) Onset After Dupilumab: Report of Two Cases and a Narrative Review of the Literature

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Abstract

Background/Objectives: Dupilumab is a fully human IgG4 monoclonal antibody targeting the interleukin-4 receptor α subunit, inhibiting interleukin-4 and interleukin-13 signalling, and suppressing type 2 inflammation. It is approved for several eosinophilic and type 2 inflammatory diseases, including chronic rhinosinusitis with nasal polyps, asthma, atopic dermatitis, eosinophilic oesophagitis, and, more recently, eosinophilic chronic obstructive pulmonary disease. Although generally well tolerated, dupilumab has been associated with peripheral eosinophilia and, rarely, eosinophil-mediated complications. This study aims to describe cases of eosinophilic granulomatosis with polyangiitis (EGPA) occurring after dupilumab initiation and to review available evidence on this association. **Methods:** We describe two cases of new-onset EGPA developing after the introduction of dupilumab therapy, analysing clinical features, laboratory findings, management, and outcomes. A narrative review of published case reports and literature addressing dupilumab-associated eosinophilia and EGPA was also performed. **Results:** Both patients developed EGPA after starting dupilumab, presenting with marked peripheral eosinophilia and systemic manifestations consistent with the disease. Clinical improvement was observed following dupilumab discontinuation and initiation of appropriate immunosuppressive treatment. The literature review identified a small number of similar reports describing EGPA onset or unmasking in temporal association with dupilumab, mainly in patients with underlying type 2 inflammatory disorders. **Conclusions:** While a causal relationship between dupilumab and EGPA remains unproven, these findings highlight the importance of clinical awareness. Dupilumab remains an effective therapy for severe type 2 inflammatory diseases; careful monitoring may allow early recognition and management of rare eosinophilic complications.



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Keywords: dupilumab; eosinophilic granulomatosis with polyangiitis; EGPA; case report

1. Introduction

Dupilumab is a fully human IgG4 monoclonal antibody targeting interleukin-4 receptor α subunit (IL-4R α), which is able to suppress type 2 inflammation by inhibiting interleukin-4 (IL-4) and interleukin-13 (IL-13) signalling [1]. It is approved for the

treatment of several eosinophilic disorders, including chronic rhinosinusitis with nasal polyps (CRSwNP), asthma, atopic dermatitis (AD), prurigo nodularis and eosinophilic esophagitis (EoE); it has also been recently approved as add-on maintenance therapy for inadequately controlled chronic obstructive pulmonary disease (COPD) and eosinophilic phenotype [2–8].

Overall, clinical trials have shown a favourable safety profile, with injection-site reactions, arthralgias, nasopharyngitis and conjunctivitis being the most common adverse events [5,9]. Rarely, case reports have described alopecia areata, facial rashes and thyroiditis [10].

Interestingly, despite its effectiveness in managing various eosinophilic diseases, there have been several studies reporting the occurrence of hypereosinophilia in patients receiving this drug [11–13], even though this finding does not seem to negatively affect treatment outcomes [14].

Different hypotheses have been put forward to explain the possible mechanism underlying the increase in absolute eosinophil count (AEC) induced by dupilumab. According to one of them, the blockade of IL-4 and IL-13 signalling leads to a reduction in serum eotaxin-3 levels and inhibits the very-late-antigen 4 (VLA-4)–vascular cell adhesion molecule-1 (VCAM-1) pathway. This results in a decreased eosinophil extravasation, ultimately leading to eosinophils being retained in the bloodstream [12]. Additionally, the inhibition of IL-4 reduces the synthesis of C-C Motif Chemokine Ligand 17 (CCL17), a type 2 cytokine produced by immune cells that is involved in eosinophil tissue migration [15–17]. Furthermore, despite the increase in circulating eosinophils, eosinophilopoiesis is not inhibited [11,12], and the eosinophils generated in the bone marrow continue to accumulate in the bloodstream [6,11]. On the contrary, another proposed mechanism involves the upregulation of interleukin-5 (IL-5) signalling [13,18], which plays a critical role in recruiting eosinophils from the bone marrow into the circulation [19].

Notably, the development of eosinophilia may occur only in the context of specific eosinophilic diseases: Wechsler et al. reported that AEC increases only in patients with asthma, CRSwNP and AD but not in patients with EoE [14].

Dupilumab-induced eosinophilia can have a variable course. According to a recent post hoc analysis [14], AEC generally declines to below baseline levels after the first 6 months of treatment in patients with asthma or CRSwNP. However, other data do not show a consistent AEC decrease [13,20,21]. Eosinophilia associated with dupilumab is in most cases, transient and asymptomatic [22,23]. Rarely, patients can develop complications related to persistent eosinophilic inflammation, such as eosinophilic pneumonia [11,24–29], eosinophilic pleural effusion [30] or eosinophilic gastritis [31]. Moreover, cases of systemic diseases—most notably eosinophilic granulomatosis with polyangiitis (EGPA)—have been reported in clinical trials [5,13,32,33].

EGPA is a rare form of anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis characterised by eosinophil-rich granulomatous inflammation and small-to-medium vessel vasculitis in the setting of severe asthma, CRSwNP and eosinophilia [34,35].

Overall, dupilumab's role in EGPA development is unclear, with available evidence supporting both clinical efficacy [36–38] and the risk of dupilumab-associated EGPA.

Herein, we report two cases of EGPA onset occurring after the initiation of therapy with dupilumab. A narrative review of published case reports and literature addressing dupilumab-associated eosinophilia and EGPA was also performed.

2. Materials and Methods

This study comprises a descriptive report of two cases of new-onset eosinophilic granulomatosis with polyangiitis (EGPA) occurring after the initiation of dupilumab therapy.

Clinical data were retrospectively collected from medical records and included demographic characteristics, underlying diseases, indication for dupilumab treatment, timing of symptom onset, clinical manifestations, laboratory findings (including peripheral eosinophil counts and immunological parameters), imaging studies, histopathological results when available, therapeutic interventions, and clinical outcomes.

In addition, a narrative review of the literature was conducted to identify previously reported cases of dupilumab-associated EGPA. A retrospective search was performed in the PubMed and Google Scholar databases using the keywords “dupilumab” in combination with “EGPA” or “Churg–Strauss”. Articles published in English were considered. Case reports and case series describing EGPA onset or exacerbation in temporal association with dupilumab treatment were included. Relevant references cited in the selected articles were also screened to identify additional reports.

Given the descriptive nature of the study, no statistical analyses were performed.

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical review and approval were waived for this study, as the manuscript reports two isolated clinical cases and a literature review, which do not constitute human subjects research, and no experimental intervention was performed. Written informed consent was obtained from both patients for publication of these case reports and any accompanying images.

3. Results

3.1. Case N. #1

In March 2024, a 68-year-old Caucasian man with a history of juvenile onset allergic asthma, CRSwNP and recurrent otitis media started dupilumab (300 mg every other week) due to insufficient symptom control with inhaled corticosteroids and long-acting beta2-agonists (LABA). Two weeks after dupilumab introduction, the patient was hospitalised for gastroenteritis and recurrence of otitis complicated by bilateral otomastoiditis requiring bilateral transtympanic drainage and antibiotic therapy. Blood tests showed an increase in CRP (45 mg/L), white blood cells (WBC) (11,000/ μ L) and AEC (2920/ μ L). One month later, he was newly admitted to our hospital, presenting with fever, fatigue, dyspnoea on mild exertion and chest pain. Blood tests showed leucocytosis with increased AEC (up to 5630/ μ L) in association with an increase in CRP (117 mg/L). Liver and renal function were within normal limits, and cardiac involvement was ruled out by assessing laboratory biomarkers (troponins, creatine kinase-MB, NT-proBNP) and performing an echocardiographic examination. On ENT evaluation, nasal crusting was observed, and otoscopy revealed minimal middle ear effusion as a result of previous otomastoiditis. A chest X-ray and a subsequent chest CT revealed multiple pseudonodular lesions in both lungs and moderate left pleural effusion, in the absence of hilar-mediastinal lymphadenopathy (Figure 1). Infectious and haematological causes were ruled out through an extensive workup. Therefore, EGPA was suspected. Immunological tests were negative, including antinuclear antibodies (ANA) and both anti-myeloperoxidase (MPO) and anti-proteinase 3 (PR3) ANCA antibodies. IgG subclasses and complement levels were within normal limits. A transbronchial biopsy revealed intense mixed inflammatory infiltrate with a significant eosinophilic component and accumulation of foam histiocytes within the alveoli, vasculitis of small arterial and venous vessels, organising pneumonia and marked fibrosis, in the absence of granulomas. The bronchoalveolar lavage showed neutrophilic and eosinophilic granulocytic alveolitis, with negative microbiological tests. A diagnosis of EGPA was made according to the 2022 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria [39] on the basis of adult-onset asthma, CRSwNP, hypereosinophilia and extravascular eosinophilic predominant inflammation

on lung biopsy. Dupilumab was discontinued, and intravenous (iv) steroid therapy was initiated, leading to progressive clinical and laboratory improvement. The patient was discharged on oral corticosteroids (OCS)—specifically prednisone 50 mg/d—and referred to our rheumatology department. Mepolizumab (300 mg subcutaneously every 4 weeks) was subsequently introduced as a maintenance therapy, allowing for a gradual tapering of corticosteroids (Figure 2). On our last evaluation in October 2025, there were no clinical or laboratory manifestations suggestive of active vasculitis, and asthma was well controlled. However, the patient continued to experience CRSwNP symptoms, for which he had recently been prescribed an anti-TLSP monoclonal antibody. He also continued therapy with mepolizumab (300 mg/month) and regular combined inhalation therapy.



Figure 1. Representative images of case #1. Chest computed tomography performed on hospital admission at EGPA onset. (A) Coronal section; (B) axial section.

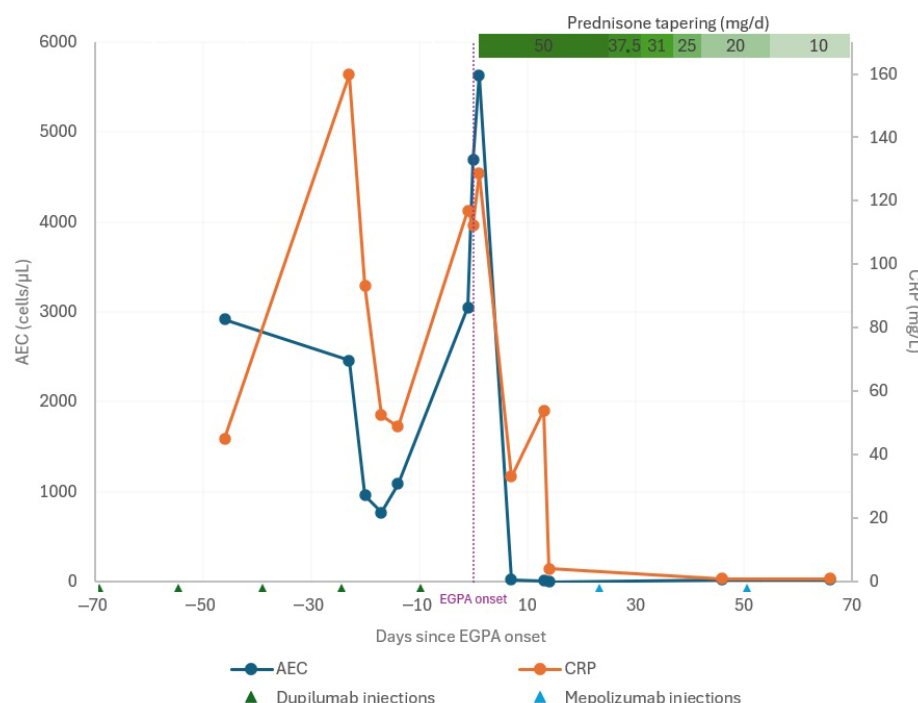


Figure 2. Graphical summary of clinical course and treatment timeline of case *n.* #1. X-axis: time since EGPA onset (days); main Y-axis: AEC (cells/μL); secondary Y-axis: CRP (mg/L). The triangles below the X-axis represent dupilumab and mepolizumab injections. The upper bar shows prednisone dosage (mg/day).

3.2. Case N. #2

A 63-year-old Caucasian man with a history of late-onset asthma and CRSwNP presented to the emergency department with respiratory failure (January 2019). Chest X-ray revealed a small parenchymal opacity in the middle right lobe. Blood tests showed an AEC of 890/ μ L with CRP within normal range. He was diagnosed with asthma exacerbation secondary to pneumonia and admitted to the Pulmonology department, where he received systemic glucocorticoids, antibiotics and combined inhalation therapy (corticosteroids and LABA). Notably, persisting migrating opacities were observed on a follow-up chest CT performed seven months after discharge (Figure 3). Therefore, a bronchoalveolar lavage was carried out, showing an eosinophil-rich fluid. Hence, a leukotriene receptor antagonist (montelukast) was introduced as an add-on therapy. One year later, owing to persistence of severe steroid-dependent asthma with increased AEC, montelukast was discontinued and benralizumab (30 mg monthly for the first 3 months, then every 2 months) was started. AEC soon normalised, and asthma control improved, while CRSwNP symptoms remained unchanged. Notably, immunological investigations performed at that time revealed positivity for MPO-ANCA at a titer approximately four times the upper limit of normal, with negative PR3-ANCA. Antinuclear antibodies (ANA) were also positive (1/160, speckled pattern).

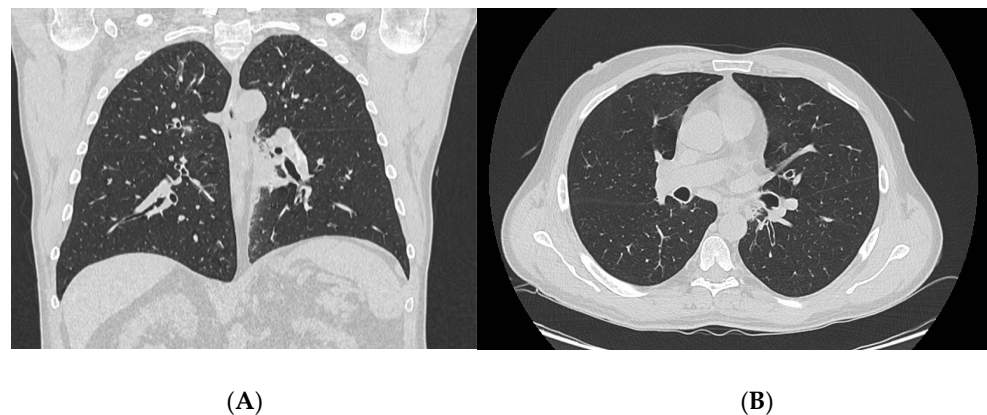


Figure 3. Representative images of case #2. Chest computed tomography performed seven months after hospital discharge. (A) Coronal section; (B) axial section.

Two years later, due to persistence of nasal congestion, rhinorrhoea and post-nasal drip, the patient was admitted to the ENT department to perform a partial nasal polypectomy. The endoscopic procedure revealed an anterior nasal septal perforation and multiple nasal polyps, whose removal would have carried a high risk of bleeding. The procedure was therefore interrupted, and an indication was given to perform the operation under general anaesthesia. In the meantime, in order to better control the nasal symptoms yet maintain a good asthma control, benralizumab was interrupted, and dupilumab was started (600 mg loading dose followed by 300 mg every other week). A few weeks after the first injection of dupilumab, the patient presented to his General Practitioner with fever, generalised weakness and diffuse arthralgias. He later developed bilateral conjunctival hyperaemia and crusty rhinitis accompanied by unintentional weight loss (−4 kgs). Blood tests performed after a total of 3 dupilumab injections revealed an AEC of 11,540/ μ L (61.6%). Dupilumab was therefore discontinued. Laboratory testing performed soon after confirmed the positivity of MPO-ANCA (67 IU/mL) with negative PR3-ANCA. CRP was markedly increased (137.3 mg/L). Serum IgE levels, cryoglobulins, complement C3 and C4 levels, and urinalysis were within the normal range. Chest X-ray did not show any parenchymal lung opacities or pleural effusion.

The patient was therefore referred to our department, presenting with persistent arthralgias, asthenia and low-grade fever. On physical examination, lung auscultation revealed diffuse fine crackles without wheezing sounds. Two small non-palpable purpuric patches were noticed on the upper limbs. Bilateral conjunctival hyperaemia was still present, possibly due to ongoing episcleritis. The patient's symptoms and clinical course were consistent with EGPA. Mepolizumab 100 mg every 4 weeks was started together with oral prednisone at 25 mg/day, leading to a rapid improvement of asthma control, systemic symptoms, and blood tests (normal CRP and AEC, negative MPO-ANCA). Prednisone was then gradually tapered over the following months (Figure 4). Over one year later, recurrent nasal obstruction and hyposmia during steroid tapering prompted escalation of mepolizumab to 300 mg every 4 weeks, with only partial benefit. On our last evaluation in November 2025, vasculitis and asthma remained well controlled, while CRSwNP symptoms persisted, and the patient was awaiting further ENT surgical intervention.

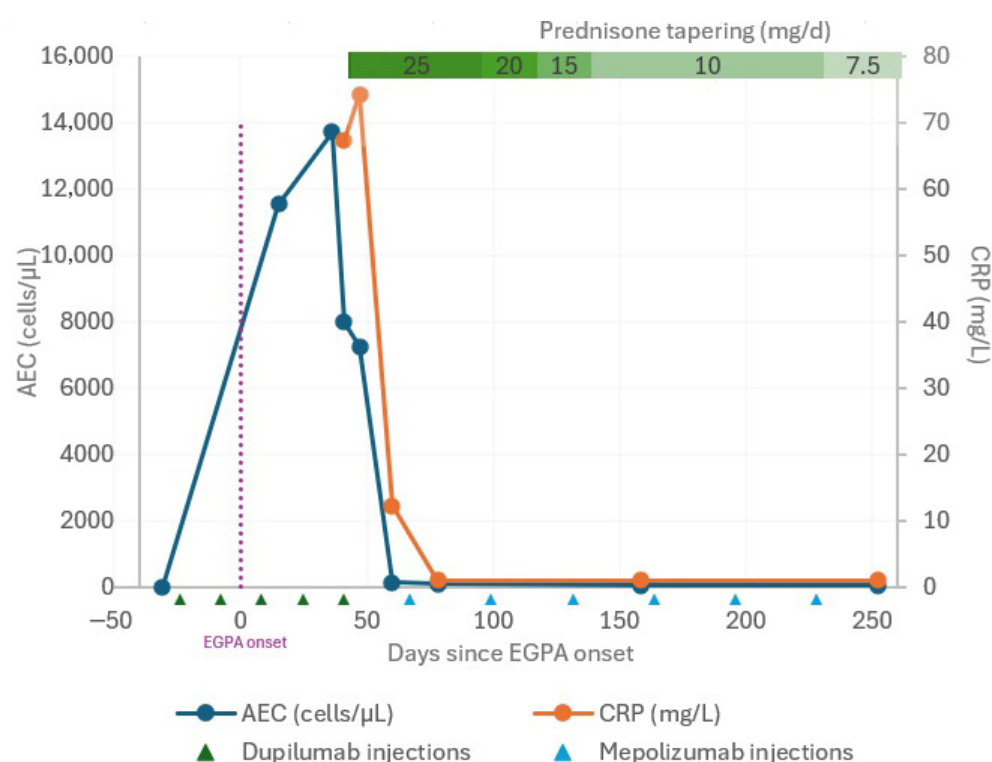


Figure 4. Graphical summary of clinical course and treatment timeline of case n. #2. X-axis: time since EGPA onset (days); main Y-axis: AEC (cells/μL); secondary Y-axis: CRP (mg/L). The triangles below the X-axis represent dupilumab and mepolizumab injections. The upper bar shows prednisone dosage (mg/day).

3.3. Review of the Literature

To the best of our knowledge, a total of 22 case reports describing the onset of eosinophilic granulomatosis with polyangiitis (EGPA) following dupilumab treatment have been published up to December 2025. These cases were identified through a retrospective literature search conducted in the PubMed and Google Scholar databases using the keywords “dupilumab” in combination with “EGPA” or “Churg–Strauss”.

Table 1 summarises the main characteristics of all published cases, including the two patients reported in the present study.

Table 1. Case reports of Eosinophil Granulomatosis with Polyangiitis (EGPA) onset after dupilumab introduction described in the literature.

N	Age at EGPA Onset	Sex	Previous Clinical Manifestations	Previous Laboratory Findings	Prior Therapy	Clinical Manifestations at EGPA Onset	Laboratory at EGPA Onset	Time of Onset After Dupilumab Introduction (Weeks)	Dupilumab Discontinuation?	Corrective Treatment
1. Anai (2022) [40]	42	M	Asthma	PR3-ANCA: + †	Inhaled LABA/LAMA OCS Omalizumab Mepolizumab Benralizumab	Fever, sinusitis, lung consolidations (transbronchial lung biopsy: eosinophilic pneumonia, possible features of healed arteritis)	AEC: normal CRP: increased MPO-ANCA: - PR3-ANCA: - IgE: normal	3	Yes	High-dose IV methylprednisolone (1000 mg/d for 3 days) followed by OCS Iv CYC (1000 mg monthly) Mepolizumab (300 mg/4w) Dupilumab reintroduced later
2. Aya (2025) [41]	53	F	Asthma, CRSwNP	Hypereosinophilia (up to 1969/μL)	NA	Orbital cellulitis and scleritis followed by GI involvement (abdominal pain, vomiting, diarrhoea) and skin rashes (skin and upper GI biopsies: perivascular eosinophilic infiltrate)	AEC: 869/μL CRP: normal MPO-ANCA: -	24	Yes	OCS Mepolizumab (300 mg/4w)
3. Barratt (2023) [42]	60	F	Asthma, CRSwNP	Hypereosinophilia (up to 1620/μL)	Benralizumab	Arthralgias, livedo racemosa-like skin rash (biopsy: eosinophilic vasculitis); left CRAO (vision loss, papilledema)	AEC: 3260/μL MPO-ANCA: + (34 IU/mL)	3	NA	High-dose prednisone Rituximab Mepolizumab
4. Eger (2021) [26]	63	F	Asthma	NA	OCS Benralizumab	Dysarthria and left-sided neurologic deficit, bilateral lung consolidations	AEC: 3940/μL ANCA: -	14	Yes	OCS Mepolizumab (300 mg/4w)
5. Fargeas (1) (2023) [43]	36	F	Asthma, CRSwNP	Eosinophilia (up to 1000/μL) MPO-ANCA: + ‡	OCS Mepolizumab Benralizumab	Mononeuritis multiplex	AEC: 1000/μL MPO-ANCA: +	33	NA	Prednisone CYC

Table 1. Cont.

N	Age at EGPA Onset	Sex	Previous Clinical Manifestations	Previous Laboratory Findings	Prior Therapy	Clinical Manifestations at EGPA Onset	Laboratory at EGPA Onset	Time of Onset After Dupilumab Introduction (Weeks)	Dupilumab Discontinuation?	Corrective Treatment
6. Fargeas (2) (2023) [43]	63	F	Asthma, CRSwNP	AEC: 400/ μ L ANCA: -	OCS Omalizumab Tralokinumab Mepolizumab	Mononeuritis multiplex, diplopia (brain MRI: ischemic-like lesions in the capsulo-lenticular area and the right caudate nucleus), erosive tracheitis (biopsy: focally dense inflammatory infiltrate of eosinophils)	AEC: 14,000/ μ L MPO-ANCA: +	16 Δ	Yes	Prednisone Rituximab
7. Hu (2023) [44]	64	F	Asthma, CRSwNP	Eosinophilia (up to 700/ μ L)	NA	Arthralgias, abdominal pain with diarrhoea, purpuric rash and tense purple bullae on upper limbs (biopsy: eosinophilic vasculitis)	AEC: 6280/ μ L p-ANCA: + (80.1 IU/mL)	8	Yes	Methylprednisolone (1 mg/kg) CYC (750 mg/m ²)
8. Ikeda (2022) [45]	71	M	Allergic rhinitis, asthma	AEC: 280/ μ L IgE: 779 IU/mL	Inhaled CS/LABA Pranlukast	General symptoms (malaise, low-grade fever), rash in lower limb, sinusitis, nasal polyps, bilateral lower leg and plantar hypoesthesia	AEC: 8379/ μ L MPO-ANCA: - IgE: 541 IU/mL	96 *	NA	OCS (1 mg/kg/d)
9. Jin (2025) [46]	62	F	Allergic rhinitis, asthma, CRSwNP, psoriasis	Hypereosinophilia (up to 3000/ μ L) ANCA: -	NA	General symptoms (fever, weight loss, arthralgias, headache), hearing loss, vision loss (orbit MRI: bilateral perineural sheath enhancement)	AEC: NA CRP: 133 mg/L	2–4	Yes	High dose iv methylprednisolone for 3 days followed by OCS Rituximab
10. Kaburaki (2025) [47]	48	F	Asthma, CRSwNP	Hypereosinophilia (up to 2098/ μ L) MPO-ANCA: + (46.1 IU/mL)	Inhaled CS/LABA	General symptoms (fever, fatigue, arthralgias), peripheral neuropathy	AEC: 11,889/ μ L CRP: 61.3 mg/L MPO-ANCA: + (125 IU/mL) IgE: 120 IU/mL	0	Yes	High-dose iv methylprednisolone followed by OCS IVIg 2 g/kg Mepolizumab (300 mg/4w)

Table 1. Cont.

N	Age at EGPA Onset	Sex	Previous Clinical Manifestations	Previous Laboratory Findings	Prior Therapy	Clinical Manifestations at EGPA Onset	Laboratory at EGPA Onset	Time of Onset After Dupilumab Introduction (Weeks)	Dupilumab Discontinuation?	Corrective Treatment
11. Kai (2023) [48]	67	F	Asthma, CRSwNP, polyarthritis, haemoptysis with GGO on chest CT scan	Hypereosinophilia (up to 12,800/ μ L) ANCA: -	Inhaled CS/LABA/LAMA OCS	General symptoms (arthralgias, fatigue), periaortitis (abdominal and back pain)	AEC: 1090/ μ L CRP: 22.5 mg/L ANCA: - IgG4: 1.9 g/L	44	Yes	OCS (0.5 mg/kg/d) Mepolizumab (100 mg/4w)
12. Matsumoto (2025) [49]	64	M	Asthma, CRSwNP	Eosinophilia (up to 948/ μ L) ANCA: - IgE: 1641 IU/mL	Inhaled CS/LABA/LAMA Leukotriene receptor antagonist Mepolizumab	Peripheral neuropathy, CRAO (sudden left visual field deficit)	AEC: 2608/ μ L ANCA: -	6	Yes	OCS (30 mg/d) Mepolizumab (100 mg/4w)
13. McDermott (2021) [50]	63	M	Asthma	NA	Mepolizumab	General symptoms (myalgias, fever, fatigue), skin plaques on extremities (biopsy: eosinophilic infiltration), eosinophilic myocarditis	AEC: increasing (54% of WBC) CRP: increased ANCA: -	24	NA	High-dose IV methylprednisolone followed by OCS CYC for remission induction followed by azathioprine as maintenance therapy
14. Milne (2022) [51]	63	M	Asthma, CRSwNP	AEC: normal	Inhaled CS/LABA OCS Mepolizumab	General symptoms (myalgias, arthralgias, fatigue), skin purpuric rash (biopsy: small-vessel vasculitis with eosinophilic infiltrate), pulmonary nodules, pleural effusion, eosinophilic myocarditis	AEC: 1100/ μ L ANCA: - IgE: normal	28	Yes	High-dose IV methylprednisolone (1000 mg/d for 3 days) followed by OCS CYC (750 mg) for remission induction followed by Azathioprine (2 mg/kg) plus mepolizumab (300 mg/4w)
15. Murag (2021) [52]	41	M	Allergic rhinitis, asthma, atopic dermatitis, CRSwNP	AEC: 10/ μ L	OCS	Bilateral lung consolidations (chest pain, dyspnoea), polyneuropathy (numbness in hands and feet)	AEC: 1250/ μ L ANCA: -	12	Yes	Steroids Mepolizumab

Table 1. Cont.

N	Age at EGPA Onset	Sex	Previous Clinical Manifestations	Previous Laboratory Findings	Prior Therapy	Clinical Manifestations at EGPA Onset	Laboratory at EGPA Onset	Time of Onset After Dupilumab Introduction (Weeks)	Dupilumab Discontinuation?	Corrective Treatment
16. Persaud (2022)[53]	58	M	CRSwNP	AEC: normal	Antihistamines Inhaled CS Short-term OCS	General symptoms (arthralgias, fatigue), left pedal oedema, bilateral lung consolidations, skin rash (biopsy: eosinophilic vasculitis), pauci-immune glomerulonephritis	AEC: 22,000/ μ L CRP: 54 mg/L MPO-ANCA: +	1–2	Yes	High-dose IV methylprednisolone for 3 days followed by OCS Rituximab
17. Suzuki (2023) [54]	63	F	Allergic rhinitis, asthma, CRSwNP, eosinophilic otitis media, eosinophilic pneumonia	Eosinophilia (up to 770/ μ L) MPO-ANCA: + (10.3 IU/mL) ** IgE: 893 IU/mL	Antihistamines Intranasal CS Inhaled CS/LABA Short-term OCS Montelukast	Right-hand numbness, rhinosinusitis, otitis, anosmia, cough, bilateral lung consolidations, facial oedema	AEC: 900/ μ L CRP: increased MPO-ANCA: + (15 IU/mL) IgE: 936 IU/mL	4	Yes	OCS CYC (750 mg for 6 courses) for remission induction, followed by Azathioprine plus Mepolizumab (300 mg/4w)
18. Tanaka (2022) [55]	50	M	Asthma, CRSwNP	NA	Inhaled CS/LABA	High-grade fever, dyspnoea and wheezing, right lung consolidation (transbronchial biopsy: interstitial eosinophilic pneumonia)	AEC: 17,400/ μ L CRP: 163 mg/L ANCA: -	20	NA	High-dose IV methylprednisolone (1000 mg/d for 3 days) followed by OCS (1 mg/kg/d)
19. Von Deimling (1) (2022) [56]	25	F	Asthma, CRSwNP	NA	OCS	General symptoms (myalgias, arthralgias), exacerbated asthma, conduction disturbances, pericardial effusion, bilateral lung consolidations, non-specific neurological symptoms	AEC: 7550/ μ L CRP: 147 mg/L ANCA-MPO: +	2	Yes	High dose IV prednisolone (250 mg/d) followed by OCS Methotrexate (12.5 mg/w) Mepolizumab (300 mg, single dose)
20. Von Deimling (2) (2022) [56]	57	F	Asthma, CRSwNP	NA	Mepolizumab	General symptoms (myalgias, arthralgias), bilateral lung consolidations, mononeuritis multiplex, skin purpuric rash, renal insufficiency with proteinuria and haematuria	AEC: 3200/ μ L CRP: 94 mg/L MPO-ANCA: +	8	Yes	IV prednisolone (100 mg/d) followed by OCS Mepolizumab (100 mg/4w) Rituximab

Table 1. Cont.

N	Age at EGPA Onset	Sex	Previous Clinical Manifestations	Previous Laboratory Findings	Prior Therapy	Clinical Manifestations at EGPA Onset	Laboratory at EGPA Onset	Time of Onset After Dupilumab Introduction (Weeks)	Dupilumab Discontinuation?	Corrective Treatment
21. Wu (2025) [57]	53	F	Asthma	Hypereosinophilia (up to 4420/ μ L) ANCA: -	Inhaled CS Leukotriene receptor antagonist	Sinusitis, lung infiltrates, peripheral neuropathic pain	AEC: NA CRP: 32.4 mg/L	2	Yes	OCS Mepolizumab (300 mg/4w)
22. Yamazaki (2022) [58]	77	F	Asthma, CRSwNP, eosinophilic pneumonia	Hypereosinophilia (up to 5967/ μ L) IgE: 918 IU/mL	Antihistamines Inhaled CS/LABA Leukotriene receptor antagonist	General symptoms (fever 38 °C, night sweating), ethmoid sinusitis, polyarthritis, fasciitis, skin rash (biopsy: vasculitis with eosinophilic infiltration)	AEC: 835/ μ L CRP: 279 mg/L MPO-ANCA: - PR3-ANCA: -	24	Yes	OCS (1 mg/kg/d)
23. Our patient #1	67	M	Asthma, CRwNP, recurrent otitis media	NA	Inhaled CS/LABA OCS	General symptoms, gastroenteritis, otitis complicated by bilateral otomastoiditis, bilateral lung consolidations and pleural effusion	AEC: 5630/ μ L CRP: 117 mg/L MPO-ANCA: -	2	Yes	IV steroid therapy followed by OCS (50 mg/d) Mepolizumab (300 mg/4w)
24. Our patient #2	68	M	Asthma, CRSwNP with nasal septal perforation	Eosinophilia (up to 1160/ μ L) MPO-ANCA: + PR3-ANCA: -	Inhaled CS/LABA/LAMA OCS Montelukast Benralizumab	General symptoms (fever, weakness, weight loss, arthralgias), bilateral conjunctival hyperaemia and crusty rhinitis	AEC: 11,540/ μ L CRP: 137 mg/L MPO-ANCA: + (67 IU/mL) IgE: 81.6 IU/mL	6	Yes	OCS (25 mg/d) Mepolizumab (100 mg/4w)

Legend: EGPA: eosinophilic granulomatosis with polyangiitis; PR3-ANCA: proteinase-3-specific antineutrophil cytoplasmic antibodies; LABA: long-acting β 2-agonists; LAMA: long-acting muscarinic antagonists; OCS: oral corticosteroids; AEC: absolute eosinophil count; CRP: C-reactive protein; MPO-ANCA: myeloperoxidase-specific antineutrophil cytoplasmic antibodies; IgE: immunoglobulin E; iv: intravenous; mg/d: milligrams per day; CYC: cyclophosphamide; mg/4w: milligrams every four weeks; CRSwNP: chronic rhinosinusitis with nasal polyps; μ L: microliters; NA: not available/not assessed; GI: gastrointestinal; CRAO: central retinal artery occlusion; ANCA: antineutrophil cytoplasmic antibodies; MRI: magnetic resonance imaging; p-ANCA: perinuclear antineutrophil cytoplasmic antibodies; mg/kg: milligrams per kilogram; mg/m²: milligrams per square metre; IU/mL: international units per millilitre; CS: corticosteroids; IVIG: intravenous immunoglobulin; GGO: ground-glass opacities; CT: computed tomography; IgG4: immunoglobulin G subclass 4; g/L: grams per litre; WBC: white blood cell count. [†] single finding, 3 years before EGPA onset. [‡] single finding, at low titre, 30 months before EGPA onset. ^Δ and 4 weeks after dupilumab discontinuation. * and 20 weeks after dupilumab discontinuation. ** single finding, 2 years prior to dupilumab introduction.

4. Discussion

The first cases of EGPA onset occurring during treatment with dupilumab have been reported as a rare adverse event in clinical trials. In 2021, the TRAVERSE study—a multicentric open-label extension study evaluating the safety and efficacy of dupilumab in patients with moderate-to-severe asthma who had previously completed a dupilumab asthma study—found that only 5 out of more than 2000 enrolled patients developed EGPA after using dupilumab [13]. More recently, the TRAVERSE Continuation Study reported no more EGPA onset cases [59].

Regarding patients with CRSwNP, the SINUS-24 and SINUS-52 trials reported only one case of EGPA during dupilumab administration and two cases in patients receiving placebo [5].

None of these trials has demonstrated a direct causal relationship between dupilumab and the development of EGPA. Patients who developed EGPA may have been misclassified prior to the study, as severe asthma or CRSwNP are often early manifestations of EGPA, in the absence of vasculitis features.

4.1. Proposed Mechanisms

The exact mechanisms through which dupilumab may trigger the development of EGPA are unknown. Since dupilumab's molecular targets appear to be less involved in the pathobiology of EGPA, a direct drug-related process is unlikely to be the primary cause of the disease. The corticosteroid-sparing effect of dupilumab might offer an explanation, as previously described with leukotriene receptor antagonists [60,61] and anti-IgE monoclonal antibodies [62]: the more rapid withdrawal of corticosteroid therapy may lead to the unmasking of a pre-existing underlying EGPA [63]. In fact, refractory asthma and CRSwNP can be both stand-alone conditions and precursor manifestations of EGPA, according to the so-called “eosinophilic march” hypothesis. It could be speculated that, in predisposed individuals, an increase in AEC, particularly when combined with rapid corticosteroid tapering, may accelerate progression along the “eosinophilic march”, thereby favouring EGPA emergence. Furthermore, although biologics targeting type 2 pathways control eosinophilic inflammation, they do not address the mechanisms underlying necrotising vasculitis, as glucocorticoids do.

On the other hand, a recent postmarketing analysis [64] suggested that the relatively high number of eosinophilic adverse events reported with dupilumab, compared with other biologics targeting type 2 inflammatory pathways—specifically omalizumab and mepolizumab—may imply a potential direct pathogenetic role of dupilumab. This could be related to the distinctive effects of dupilumab on eosinophil biology. As previously anticipated, dupilumab has been associated with the possible development of peripheral eosinophilia through several mechanisms, including inhibition of eosinophil tissue migration via blockade of the VLA-4/VCAM-1 pathway, a compensatory increase in IL-5 production, and the lack of direct suppression of eosinopoiesis in the bone marrow. In genetically predisposed individuals, the development of eosinophilia could be the trigger leading to EGPA emergence. However, dupilumab-associated eosinophilia appears to occur predominantly in patients with specific underlying diseases, namely asthma, CRSwNP, and AD, while it has not been consistently described in other disorders, including EoE or COPD with eosinophilic phenotype [65]. This “disease-specific pattern” suggests that the development of eosinophilia—and possibly EGPA—may not be solely drug-driven but rather influenced by pre-existing immune dysregulation and disease-specific type 2 inflammatory pathways.

Overall, it remains unclear whether dupilumab acts as a direct trigger of EGPA or whether it accelerates disease emergence in predisposed individuals through modulation

of eosinophil trafficking and survival. It could be speculated that, rather than acting as a direct trigger, dupilumab may modulate eosinophil biology differently from other biologics targeting type 2 inflammation; as this effect seems to be confined to patients with specific underlying diseases, a complex interplay between drug-related mechanisms and disease-specific immune pathways is conceivable.

4.2. Timing of EGPA Onset After Dupilumab Introduction and Possible Risk Factors

Based on published case reports, the timing of EGPA onset after dupilumab administration is heterogeneous (1 week–2 years; median (IQR): 8 weeks [3–24]): 13 patients developed EGPA within 8 weeks of starting dupilumab therapy (including our patients #1 and #2), while the remaining patients developed EGPA after more than 8 weeks, including two patients who developed EGPA after having already discontinued dupilumab [43,45].

Currently, there are no validated predictive factors for the development of EGPA in patients with asthma or CRSwNP starting dupilumab; however, some risk factors should be taken into account as potential markers of disease onset.

1. History of multiple eosinophilic disorders

Patients who developed EGPA following the introduction of dupilumab in clinical trials had a previous history of eosinophil-mediated disorders [13], including allergic rhinitis, late-onset eosinophilic asthma, CRSwNP or ear disorders. However, it is difficult to predict which condition will progress to EGPA in the absence of findings, suggesting the presence of an underlying vasculitis. Therefore, when the introduction of dupilumab worsens a pre-existing asthma or sinusitis or is followed by the development of systemic symptoms, the possibility of an underlying EGPA should be taken into consideration.

According to published case reports, most patients who developed EGPA after dupilumab introduction had severe asthma and/or CRSwNP; two patients reported a previous history of eosinophilic otitis media [58] (our patient #2), four of allergic rhinitis [45,46,52,54], two of eosinophilic pneumoniae [54,58], while only one had a previous diagnosis of AD [52].

2. AEC kinetics

Regarding the relationship between the development of eosinophilia following dupilumab introduction and the risk of EGPA onset, Kushima et al. reported that AEC keeps rising within 6 months of dupilumab treatment in those who have a higher chance of developing EGPA [1]. This suggests that persistently elevated AEC is associated with a higher risk than transient eosinophilia.

Moreover, patients who develop an AEC greater than 1500/ μ L after 3 months from dupilumab introduction seem to show a higher incidence of EGPA in the future compared with those who do not reach this peak value. The same difference was not seen after 6 months of using dupilumab. Under this perspective, regular AEC monitoring is advisable during dupilumab administration.

3. Previous therapy with anti-IL5/R agents

According to published case reports, 10 patients developed EGPA after switching biologics from anti-IL5/R antibodies to dupilumab [24,43,45,46,52,54,63,65], (our patient #2).

It has been hypothesised that switching from biologics blocking the anti-IL5 pathway to dupilumab may increase the risk of EGPA onset because of a rebound effect on eosinophilic inflammation due to interactions with alternative immunological pathways [1].

Notably, previous exposure to anti-IL5/R agents has been reported to affect subsequent AEC kinetics after dupilumab initiation. Numata et al. observed that AEC peaked at approximately 3 months in patients who had not received anti-IL5/R agents prior to

dupilumab, while in those who had previously received these biologics, AEC levels peaked around 6 months, suggesting a delayed AEC peak in the second group [21]. Likewise, Kushima et al. reported that AEC declined at 6 months after dupilumab administration in patients who had not received prior biologics, but this was not the case in those who had received biologics before [1]. Overall, these observations suggest that prolonged AEC monitoring may be warranted in such patients.

4. Previous ANCA positivity

There is an increasing amount of evidence suggesting that EGPA clinical phenotypes tend to segregate in accordance with ANCA status. ANCA-negative patients tend to experience more eosinophil-driven manifestations (e.g., lung infiltrates, cardiomyopathy, gastrointestinal symptoms), whereas proper vasculitis features (e.g., palpable purpura, peripheral neuropathy, more rarely pulmonary-renal syndrome) are more frequently found in the ANCA-positive subset of EGPA [66,67].

According to published case reports, five patients [40,43,47,54], (our patient #2) had a previous finding of ANCA positivity (1 PR3-ANCA, 4 MPO-ANCA) at varying time points prior to dupilumab initiation.

ANCA testing was negative in five additional cases [43,46,48,49,57], whereas for the remaining patients, ANCA status was not available.

After dupilumab introduction, ten patients presented ANCA positivity (nine with MPO specificity, one only reported as positive ANCA with immunofluorescence perinuclear pattern) [47–49,52,56,63,65] (our patient #2).

Three out of four patients with previous documented ANCA positivity had it confirmed after EGPA onset [43,47,54].

Overall, even though according to published literature only 30–40% of EGPA cases are ANCA-positive [67], performing an ANCA-screening in patients with previous eosinophilic disorders before the initiation of dupilumab may be considered in order to identify those at higher risk of underlying EGPA.

4.3. Dupilumab-Associated EGPA Treatment

How to address dupilumab-associated eosinophilic adverse events is still to be determined. Options may include stopping dupilumab and/or adding corticosteroids or drugs targeting IL-5 pathway.

To the best of our knowledge, there are currently no recommendations addressing the optimal management of patients who experience EGPA onset following dupilumab introduction.

In a real-life setting, all published cases of dupilumab-related EGPA reported treatment with corticosteroids (including iv administration in 10 patients). Rituximab (RTX) [42,43,46,53,56], and cyclophosphamide (CYC) [40,43,44,50,51], were both necessary in five cases, whereas methotrexate (MTX) and azathioprine (AZA) were introduced as add-on maintenance therapy in one [56,59] and three [50,51,54,57,58], cases respectively. In one case [47] high-dose IV immunoglobulins (IVIG) were used to treat residual neuropathy. Moreover, mepolizumab was introduced in 15 patients [24,42,45,46,49,52,56–58,65–67] (our patients #1 and #2); seven of them had previously received anti-IL5 pathway blocking therapies: three mepolizumab only [49,51,56], three benralizumab only [24,52] (our patient #2), one both mepolizumab and benralizumab [40].

Notably, in the case reported by Anai et al. [40], dupilumab was first discontinued but later reintroduced concomitantly with mepolizumab owing to insufficient asthma control, with significant benefit. Interestingly, there have been a few reports in the literature of successful outcomes with the combination of anti-IL5 therapies and dupilumab in patients with EGPA [25,68–70]. In fact, although anti-IL5 therapies have proven effective

for both induction of remission and maintenance therapy in patients with EGPA with non-organ or life-threatening manifestations [71], the suppression of a single cytokine pathway may not be sufficient to control upper respiratory or cutaneous manifestations [72,73]. This can be attributed to the complexity of EGPA pathobiology. It has been speculated that in patients with elevated fractional exhaled nitric oxide (FeNO), inhibiting the IL-4/13 pathway may be beneficial, while targeting the IL-5 pathway may be more effective for those with predominant eosinophilic inflammation [40]. Therefore, the blockade of both IL-5 and IL-4/13 pathways can lead to a good control of challenging-to-treat EGPA symptoms, such as upper airway and cutaneous manifestations [5]. According to the reported cases of combined therapy, dupilumab was able to control CRSwNP symptoms in four cases [25,68–70] and concurrent AD in one [74]. A case series recently presented as an abstract at ACR Convergence 2025 reported 13 patients receiving a combination therapy (anti-IL-5/R agent plus dupilumab) for at least 3 months; nine patients received add-on dupilumab on top of anti-IL-5/R therapy for uncontrolled ENT/asthma symptoms, whereas in the remaining four cases an anti-IL-5/R drug was added to ongoing dupilumab for drug-induced eosinophilia plus vasculitis relapse and/or uncontrolled ENT/asthma symptoms. At last available follow up, eight patients had achieved a complete response (defined as BVAS = 0 and prednisone-equivalent dose $\leq$ 4 mg/d) and two patients a partial response (defined as BVAS = 0 and prednisone-equivalent dose $>$ 4 mg/d) [75]. Overall, no worrisome adverse events related to the combination treatment have been observed during follow-up. These data support what has already been reported in a literature review by Martins-Martinho et al. [68] which included 15 patients who underwent this dual therapy for different diseases (severe asthma, hypereosinophilic syndrome, allergic bronchopulmonary aspergillosis).

However, further research is necessary to confirm the long-term efficacy and safety of combined biologic therapies in EGPA.

5. Conclusions

The association between dupilumab administration and subsequent EGPA onset remains unclear. Several reports suggest that dupilumab may trigger an increase in AEC and potentially lead to the development of eosinophilic disorders, including EGPA. Nevertheless, it cannot be ruled out that dupilumab merely facilitates the emergence of latent EGPA through the discontinuation or reduction in corticosteroids, particularly in patients initiating this drug for uncontrolled asthma and/or CRSwNP. Moreover, most cases of eosinophilia following dupilumab introduction are transient and not clinically meaningful. Given this drug's proved efficacy in treating severe respiratory diseases—specifically CRSwNP and asthma—this possible adverse event should not discourage its prescription.

On the other hand, awareness of the potential for severe systemic complications mediated by eosinophils is mandatory when initiating dupilumab; this risk, albeit remote, should not be overlooked. It is essential to bear in mind that this risk seems to be higher when switching from an anti-IL5/R agent to dupilumab.

Overall, prior to initiating dupilumab it is advisable to rule out the presence of features suggesting an underlying systemic disease, therefore the possibility of a pre-existent EGPA. Physicians should be aware of vasculitis red flags such as fever, arthralgias, neurologic disturbances or skin purpuric rash in patients with refractory asthma or CRSwNP. Checking AEC and ANCA status is also advisable. Should suggestive clinical and/or laboratory manifestations (i.e., AEC $>$ 1500/ μ L, ANCA+) be present, it is advisable to perform instrumental tests such as chest imaging, respiratory function tests, echocardiogram and neurologic evaluation to rule out a systemic involvement. In case of a baseline AEC $>$ 1500/ μ L an anti-IL-5/IL-5R agent is preferable [76]. This approach is also supported by GINA's Global

Strategy for Asthma Management and Prevention, last updated in 2025, which specifically states that dupilumab is not advised in patients with current or past blood eosinophil counts $\geq 1500/\mu\text{L}$ [77]. Moreover, it is important to underline that the 2022 ACR/EULAR criteria for EGPA are classification criteria intended for research purposes and cannot replace comprehensive clinical evaluation. Diagnosis of EGPA relies on the integration of clinical features, laboratory findings, imaging, and—when feasible—histological assessment. Our cases illustrate that certain pre-existing findings—such as MPO-ANCA positivity or structural nasal changes such as nasal septum perforation—may serve as warning signs alerting clinicians to the potential presence of latent or evolving EGPA. These observations reinforce the need for careful baseline assessment before starting dupilumab, particularly in patients with severe asthma or CRSwNP and any features suggestive of eosinophilic systemic disease. Educating rheumatologists and other specialists, such as ENT specialists and dermatologists, about vasculitis red flags is crucial to optimise patient safety.

If AEC rises significantly and/or vasculitis symptoms emerge during dupilumab treatment, discontinuation of the drug and introduction of corticosteroid therapy are advisable. Nevertheless, combination therapy with an anti-IL5/R agent may lead to optimal symptom control.

Additional investigations are required to further clarify the association between dupilumab and the onset of EGPA, as well as to identify potential biomarkers useful for risk stratification and optimal management.

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Abbreviations

The following abbreviations are used in this manuscript:

AEC	Absolute eosinophil count
ANCA	Antineutrophil cytoplasmic antibodies
CRP	C-reactive protein
CRSwNP	Chronic rhinosinusitis with nasal polyps
CS	Corticosteroids
CYC	Cyclophosphamide
CT	Computed tomography
EGPA	Eosinophilic granulomatosis with polyangiitis

GI	Gastrointestinal
GGO	Ground-glass opacities
IgE	Immunoglobulin E
IgG4	Immunoglobulin G subclass 4
IVIG	Intravenous immunoglobulin
LABA	Long-acting β 2-agonists
LAMA	Long-acting muscarinic antagonists
MPO-ANCA	Myeloperoxidase-specific antineutrophil cytoplasmic antibodies
NA	Not available/not assessed
MRI	Magnetic resonance imaging
OCS	Oral corticosteroids
p-ANCA	Perinuclear antineutrophil cytoplasmic antibodies
PR3-ANCA	Proteinase-3-specific antineutrophil cytoplasmic antibodies
WBC	White blood cell count
CRAO	Central retinal artery occlusion

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