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Dupilumab for relapsing or refractory sinonasal and/or asthma manifestations in eosinophilic granulomatosis with polyangiitis: a European retrospective study

Berengere Molina ¹, Roberto Padoan,² Maria Letizia Urban,³ Pavel Novikov,⁴ Marco Caminati,⁵ Camille Taillé,⁶ Antoine Néel,⁷ Laurence Bouillet,^{8,9} Paolo Fraticelli,¹⁰ Nicolas Schleinitz,¹¹ Christine Christides,¹² Laura Moi,¹³ Bertrand Godeau,¹⁴ Ann Knight,¹⁵ Jan Walter Schroeder,¹⁶ Sylvain Marchand-Adam,¹⁷ Helder Gil,¹⁸ Vincent Cottin ¹⁹, Cécile-Audrey Durel,²⁰ Elena Gelain,²¹ Boris Lerais,²² Marc Ruivard,²³ Matthieu Groh ²⁴, Maxime Samson ^{25,26}, Luca Moroni,²⁷ Jens Thiel,^{28,29} Anna Kernder,³⁰ Jan Willem Cohen Tervaert,^{31,32} Giulia Costanzo,³³ Marco Folci,³⁴ Sonia Rizzello,³⁵ Pascal Cohen,³⁶ Giacomo Emmi ^{3,37}, Benjamin Terrier ¹

Handling editor Josef S Smolen

For numbered affiliations see end of article.

Correspondence to

Dr Benjamin Terrier, Department of Internal Medicine, Hospital Cochin, Paris 75014, Île-de-France, France; benjamin.terrier@aphp.fr

ABSTRACT

Background Eosinophilic granulomatosis with polyangiitis (EGPA) is often associated with glucocorticoid-dependent asthma and/or ear, nose and throat (ENT) manifestations. When immunosuppressants and/or mepolizumab are ineffective, dupilumab could be an option. We describe the safety and efficacy of off-label use of dupilumab in relapsing and/or refractory EGPA.

Patients and methods We conducted an observational multicentre study of EGPA patients treated with dupilumab. Complete response was defined by Birmingham Vasculitis Activity Score (BVAS)=0 and prednisone dose ≤ 4 mg/day, and partial response by BVAS=0 and prednisone dose > 4 mg/day. Eosinophilia was defined as an eosinophil count $> 500/\text{mm}^3$.

Results Fifty-one patients were included. The primary indication for dupilumab was disabling ENT symptoms in 92%. After a median follow-up of 13.1 months, 18 patients (35%) reported adverse events (AEs), including two serious AEs. Eosinophilia was reported in 34 patients (67%), with a peak of $2195/\text{mm}^3$ (IQR 1268–4501) occurring at 13 weeks (IQR 4–36) and was associated with relapse in 41%. Twenty-one patients (41%) achieved a complete response and 12 (24%) a partial response. Sixteen (31%) patients experienced an EGPA relapse while on dupilumab, which was associated with blood eosinophilia in 14/16 (88%) patients. The median eosinophil count at the start of dupilumab was significantly lower in relapsers than in non-relapsers, as was the median time between stopping anti-IL-5/IL-5R and switching to dupilumab.

Conclusion These results suggest that dupilumab may be effective in treating patients with EGPA-related ENT manifestations. However, EGPA flares occurred in one-third of patients and were preceded by eosinophilia in 88%, suggesting that caution is required.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Interleukin (IL)-5/IL-5R-targeted therapies may be ineffective in some patients, particularly those with ear, nose and throat manifestations, and dupilumab may be an option.

WHAT THIS STUDY ADDS

⇒ Twenty-one percent (41%) of patients treated with dupilumab achieved a complete response and 12 (24%) achieved a partial response.
⇒ Thirty-five percent (35%) of patients reported adverse events, mainly mild to moderate.
⇒ Eosinophilia was reported in 67% and was associated with clinical relapse in 41%.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Dupilumab is an interesting alternative option for the treatment of disabling sinonasal manifestations in eosinophilic granulomatosis with polyangiitis, but should be used with caution.

INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA) is the rarest antineutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) with a prevalence of 10.7–17.8 per million.^{1–3} EGPA is characterised by blood and tissue eosinophilia, asthma, ear, nose and throat (ENT) and systemic manifestations involving the lungs, peripheral nerves, skin and/or heart.^{4,5} Between 10% and 40% of EGPA patients have ANCA against myeloperoxidase (MPO), usually associated with glomerulonephritis and multiple mononeuropathy, whereas ANCA negative patients are more likely to develop cardiomyopathy.^{5–10}

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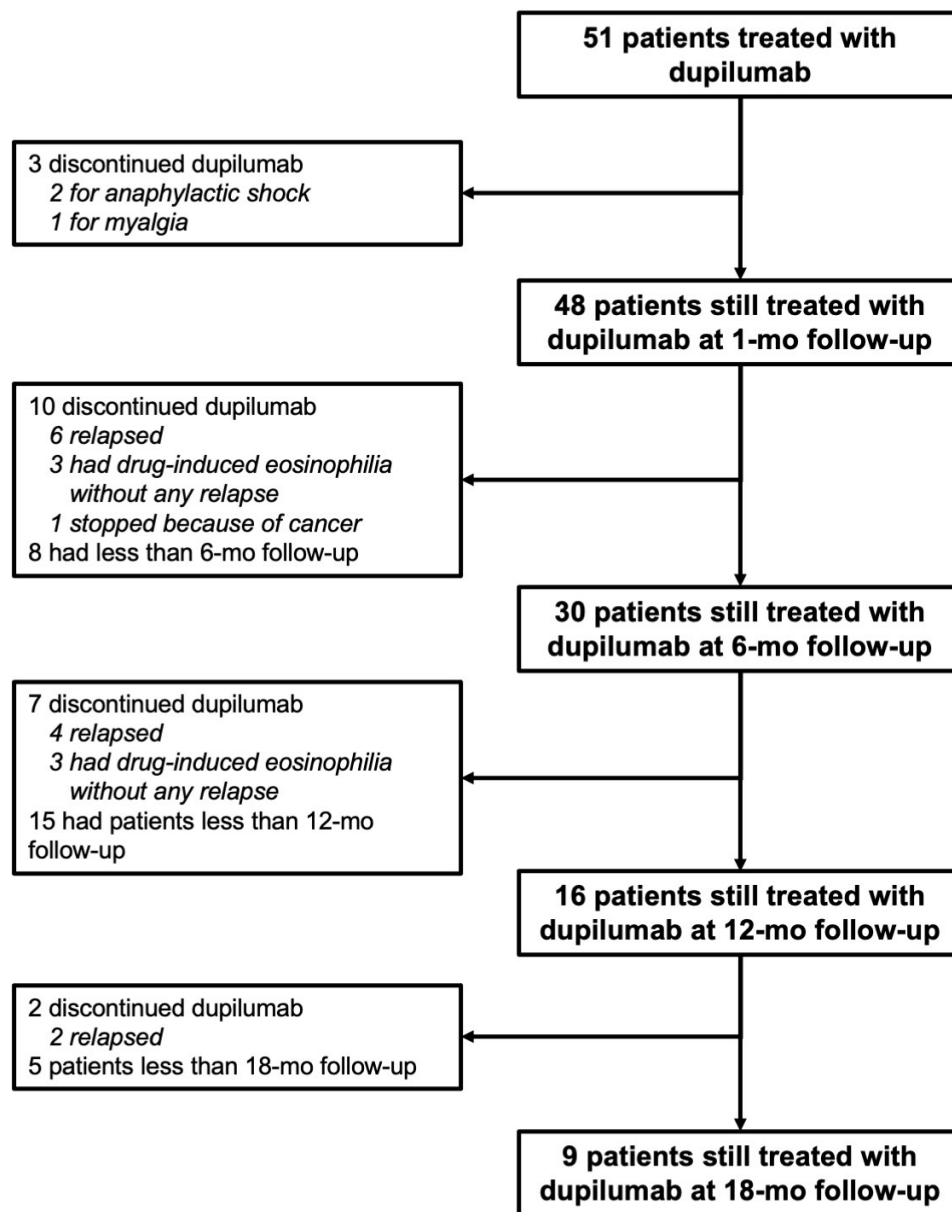


Figure 1 Flow chart describing the 51 patients treated with dupilumab from initiation to 18 months of follow-up.

Recent European Alliance of Associations for Rheumatology recommendations for the management of AAV address the treatment of EGPA.^{11 12} For the induction of remission in new-onset or relapsing EGPA with organ-threatening or life-threatening manifestations, a combination of glucocorticoids (GCs) and cyclophosphamide is recommended. In contrast, for EGPA patients without organ-threatening or life-threatening manifestations, treatment with GCs alone is recommended. However, a significant proportion of patients still experience relapses of vasculitis and/or GC-dependent asthma and/or disabling ENT symptoms, which can persist in approximately half of patients.¹³ Moreover, long-term use of GCs is associated with significant adverse events (AEs). The new recommendations also address the role of mepolizumab, an anti-interleukin (IL)-5 monoclonal antibody, and recommend its use in patients with relapsing or refractory EGPA without active organ-threatening or life-threatening disease.^{12 14} However, in routine care, the efficacy of mepolizumab in nasal polyposis can sometimes be disappointing, warranting the evaluation of other alternatives, especially when inhaled corticosteroids or surgery are not appropriate or feasible.

Dupilumab, a human monoclonal antibody that binds IL-4R α and inhibits the signalling of both IL-4 and IL-13, is approved for both the treatment of severe asthma associated with eosinophilia $>150/\text{mm}^3$ and/or Fractional exhaled Nitric Oxide >20 ppb,^{15–17} and chronic rhinosinusitis with nasal polyps (CRSwNP),¹⁸ raising the question of its safety and efficacy in relapsing or refractory EGPA. However, some cases of dupilumab-induced eosinophilia and EGPA have been reported in the literature^{15 17 18} and the risk–benefit ratio of this approach is discussed.

The aim of this work is to describe the safety and efficacy of the off-label use of dupilumab for the treatment of relapsing or refractory EGPA.

Patients and methods

Patients

We conducted a retrospective multicentre European study in patients with EGPA who satisfied the American College of Rheumatology¹¹ classification criteria¹⁹ and received dupilumab for

Table 1 Characteristics of 51 patients at diagnosis of EGPA and previous treatments received before the use of dupilumab

Demographic characteristics	Patients (n=51)
Female, n (%)	30 (59)
Age, median (IQR)	52 (45–57)
Characteristics at EGPA diagnosis	
Asthma, n (%)	51 (100)
Serum eosinophil count >1000/mm ³	50 (98)
Sinonasal involvement, n (%)	49 (96)
Pulmonary infiltrate, n (%)	35 (69)
Neuropathy, n (%)	26 (51)
Mononeuritis, n (%)	16 (31)
Polyneuritis, n (%)	10 (20)
Eosinophil-rich infiltrates, n (%)	17 (33)
General signs, n (%)	27 (53)
Musculoskeletal manifestations, n (%)	25 (49)
Skin involvement, n (%)	21 (41)
Cardiac involvement, n (%)	11 (22)
Central nervous system involvement, n (%)	5 (10)
Digestive involvement, n (%)	4 (8)
Renal involvement, n (%)	3 (6)
Ocular involvement, n (%)	2 (4)
BVAS, median (IQR)	13 (10–18)
ANCA positive, n (%)	19 (37)
Serum eosinophil count/mm ³ , median (IQR)	3600 (1980–7000)
Previous treatments	
No of previous treatments before dupilumab, median (IQR)	2 (1–3)
Prednisone, n (%)	51 (100)
Methylprednisolone pulses, n (%)	18 (35)
Azathioprine, n (%)	20 (39)
Methotrexate, n (%)	15 (29)
IV cyclophosphamide, n (%)	13 (25)
Oral cyclophosphamide, n (%)	3 (6)
Intravenous immunoglobulins, n (%)	3 (6)
Mycophenolate mofetil, n (%)	2 (4)
Cotrimoxazole, n (%)	2 (4)
Ciclosporin, n (%)	2 (4)
Mepolizumab, n (%)	26 (51)
Dose of 100 mg/4 weeks, n	15/26
Dose of 300 mg/4 weeks, n	3/26
Dose not available, n	8/26
Benralizumab, n (%)	16 (31)
Dose of 30 mg/8 weeks, n	6/16
Dose of 30 mg/4 weeks for 8 weeks followed by 30 mg/8 weeks, n	5/16
Dose not available, n	5/16
Rituximab, n (%)	11 (22)
Omalizumab, n (%)	5 (10)
Reslizumab, n (%)	1 (2)

ANCA, antineutrophil cytoplasm antibody; BVAS, Birmingham Vasculitis Activity Score; EGPA, eosinophilic granulomatosis with polyangiitis.

relapsing or refractory EGPA. Relapsing disease was defined as active vasculitis (Birmingham Vasculitis Activity Score, BVAS>0) or active asthma symptoms or worsening sinonasal manifestations requiring an increase in oral GCs dose. Refractory disease was defined as the inability to reduce GCs below 7.5 mg/day due to active disease while tapering prednisone.

Table 2 Characteristics of EGPA at initiation of dupilumab

Indication for dupilumab	Patients (n=51)
Uncontrolled ENT manifestations, n (%)	47 (92)
Nasal polyposis	32 (63)
Rhinosinusitis	32 (63)
Frequent sinonasal infections (>2/year)	10 (20)
High-GCs dependency, n (%)	29 (57)
Prednisone threshold median (IQR), mg/day	15 (10–20)
Uncontrolled asthma, n (%)	27 (53)
No of flare-ups in the last 6 months, median (IQR), n	6 (3–15)
Disease characteristics at dupilumab initiation	
Pulmonary involvement, n (%)	34 (67)
Asthma	34 (67)
Pulmonary infiltrates	3 (6)
ENT involvement, n (%)	47 (92)
Disabling nasal obstruction	42 (82)
Anosmia	41 (80)
Rhinorrhoea	31 (61)
Musculoskeletal disorders, n (%)	4 (8)
Cutaneous involvement, n (%)	2 (4)
Cardiac manifestations, n (%)	2 (4)
Gastrointestinal involvement, n (%)	1 (2)
Peripheral neuropathy, n (%)	1 (2)
BVAS, median (IQR)	2 (1–4)
Eosinophil count, median (IQR), /mm ³	375 (79–793)
Positive ANCA, n (%)	9 (18)
Treatments associated with dupilumab	
Methotrexate, n (%)	5 (10)
Azathioprine, n (%)	3 (6)
Cotrimoxazole, n (%)	1 (2)
Mycophenolate mofetil, n (%)	1 (2)

ANCA, antineutrophil cytoplasm antibody; BVAS, Birmingham Vasculitis Activity Score; EGPA, eosinophilic granulomatosis with polyangiitis; ENT, ear, nose and throat; GCs, glucocorticoids.

Assessment of clinical characteristics

Clinical and biologic data were collected retrospectively at the time of EGPA diagnosis, before treatment, at initiation of dupilumab, and during follow-up, using a standardised case report form. Clinical and biological evaluations included assessment of disease manifestations using the BVAS version 3,²⁰ determination of eosinophil count, C reactive protein and serum creatinine level, ANCA titre and specificity, urine analysis to screen for haematuria and proteinuria, forced expiratory volume in 1 s (FEV1) and FEV1/forced vital capacity, and treatment characteristics, at days 0 and 15, months 1, 3 and 6, and then every 6 months until the last follow-up. Finally, we collected data on relapses and AEs. Eosinophilia was defined as an eosinophil count greater than 500/mm³.

Response to therapy

Clinical response was defined by analysing the course of changes in vasculitis manifestations, asthma and ENT manifestations, and prednisone dose. Complete response was defined as the absence of asthma, ENT and vasculitis manifestations (BVAS of 0) and an equivalent prednisone dose ≤4 mg/day. Partial response was defined as the absence of asthma, ENT and vasculitis manifestations (BVAS of 0) and an equivalent prednisone dose >4 mg/day. Systemic relapse during dupilumab was defined as the recurrence

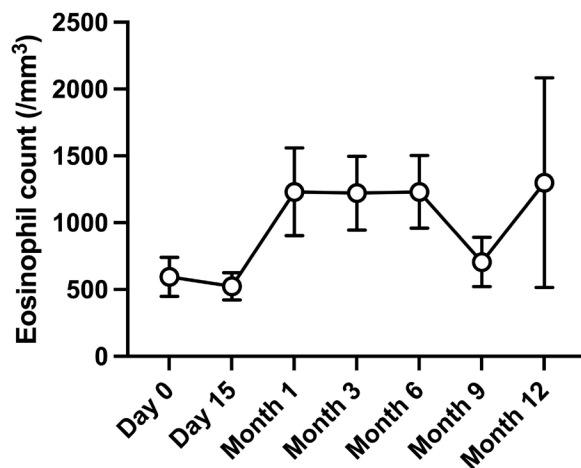
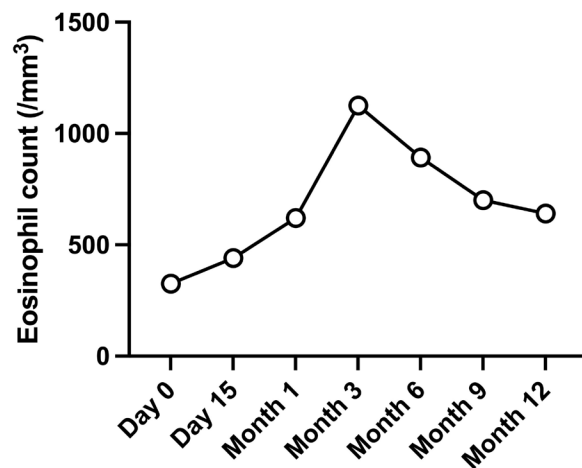
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Figure 2 Evolution of eosinophil count in patients treated with dupilumab. (A) The kinetics of eosinophil count in all patients (expressed as mean and SE of mean). (B) The kinetics of eosinophil count only in patients who experienced eosinophilia (expressed as median).

or new onset of any extrarespiratory manifestation attributable to active disease and included as a BVAS item.

STATISTICAL ANALYSIS

Data are expressed as the mean $\pm$ SD or median with IQR as appropriate for continuous variables, and number (percentage) for categorical variables. We used the Wilcoxon matched pairs test ($p < 0.05$ was considered significant). Graphical and statistical analyses were performed using GraphPad Prism V.8.0.

RESULTS

Patient characteristics

Fifty-one patients were included in the study (figure 1). The median age was 52 years (IQR 45–57) and 59% were female. All patients (100%) had asthma at the time of EGPA diagnosis and almost all (98.0%) had eosinophilia above 1000/mm³. Patient characteristics and previous treatments are summarised in table 1. Dupilumab was mainly used as third-line therapy.^{2,4} Thirty-three (65%) patients received at least one anti-IL-5/IL-5R therapy prior to dupilumab, including mepolizumab in 26 (51%), benralizumab in 16 (31%) and reslizumab in 1 (2%).

EGPA manifestations requiring initiation of dupilumab

Characteristics of EGPA patients and concomitant treatments at initiation of dupilumab are summarised in table 2. The indications for dupilumab were disabling ENT manifestations in 47 cases (92%), high-dose GC-dependency in 29 (57%) and poorly controlled asthma in 27 (53%). Dupilumab was administered concomitantly with immunosuppressive agents in 9 patients, including methotrexate (n=5), azathioprine (n=3) and mycophenolate mofetil (n=1).

Dupilumab was mainly used at a loading dose of 600 mg followed by 300 mg every 2 weeks (88%). Five patients received other regimens: 300 mg every 2 weeks without a loading dose, injection of 200 mg every 2 weeks. Median follow-up after starting dupilumab was 13.2 (5.4–17.8) months.

Safety of dupilumab

Eighteen patients (35%) reported clinically relevant AEs, most of which were mild to moderate: headache (n=4), injection-site reactions (n=3), myalgia (n=3), arthralgia (n=2), influenza-like syndrome (n=2), cough (n=1), cystitis (n=1), rhinitis (n=1),

conjunctivitis (n=1), hand paresthesia (n=1) and psoriasis exacerbation (n=1). Two patients experienced non-fatal anaphylactic shock.

Eosinophilia was reported in 34 patients (67%) with a median peak eosinophil count of 2195/mm³ (IQR 1268–4501) occurring after a median treatment duration of 13 weeks (IQR 4–36) (figure 2). Eosinophilia was asymptomatic in 14/34 (41%) cases, associated with EGPA relapse in 14 (41%) cases, and associated with symptoms unrelated to EGPA according to physician assessment in 6 (18%). Dupilumab was discontinued in 16 (47%) patients who developed eosinophilia, including 14 symptomatic patients and 2 patients who were asymptomatic yet but stopped dupilumab because of the high blood eosinophil counts. Of the cohort of 34 patients who experienced eosinophilia, 16 had their prednisone dose reduced, while 18 either maintained a stable prednisone dose or did not take prednisone at all. We also observed no difference in prednisone reduction between patients with and without eosinophilia (data not shown).

Efficacy of dupilumab

Twenty-one patients (41%) achieved a complete response and 12 (24%) achieved a partial response. Fourteen patients (27%) did not achieve either complete or partial response, while treatment efficacy was not assessable due to early treatment discontinuation in the four remaining patients. The median prednisone dose was 8 mg/day (5; 13.8) at the start of dupilumab and decreased to 5 mg/day (2.5; 7.5) at 1 month ($p = 0.001$ compared with day 0), 5 mg/day (0; 8) at 3 months ($p = 0.0003$ compared with day 0), 3.5 mg/day (0; 5) at 6 months ($p = 0.003$ compared with day 0) and 2.5 mg/day (0; 5) at 12 months ($p = 0.04$ compared with day 0) (figure 3A). Only eight patients were able to stop prednisone completely. Median BVAS was 2^{1,4} at the start of dupilumab and decreased to 0 (0; 2) at 1 month ($p < 0.0001$ compared with day 0), 0 (0; 1) at 3 months ($p < 0.0001$ compared with day 0), 0 (0; 2) at 6 months ($p = 0.001$ compared with day 0) and 0 (0; 1.5) at 12 months ($p = 0.01$ compared with day 0) (figure 3B). Median FEV1 was 85% (71; 92) (available in 25 patients) at the start of dupilumab and increased to 92% (79; 103) (available in 14 patients) at 3 months ($p = 0.04$ compared with day 0), 90% (69; 103) (available in 15 patients) at 6 months ($p = 0.04$ compared with day 0) and 79% (68; 98) (available in 8 patients) at 12 months ($p = 0.64$ compared with day 0) (figure 3C).

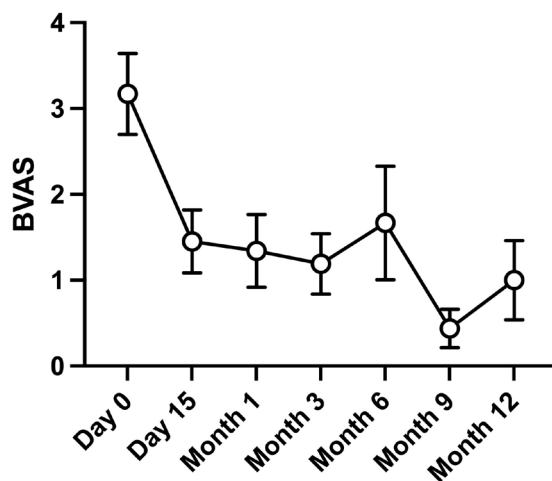
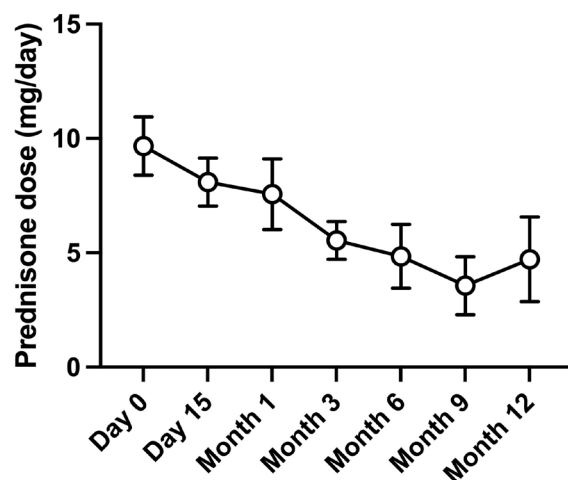
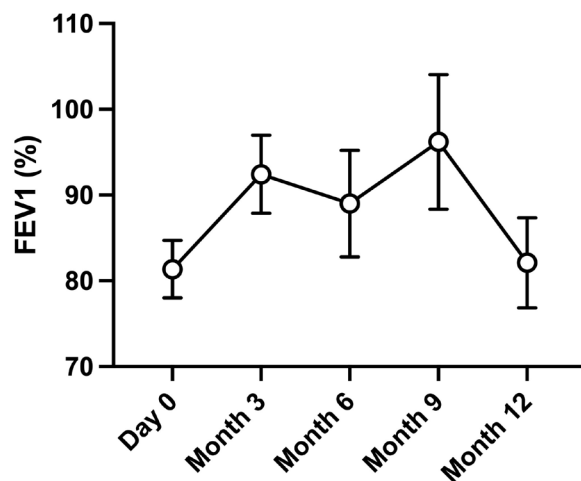
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Figure 3 Evolution of disease activity, prednisone dose and force expiratory volume in patients treated with dupilumab. Patients with EGPA were assessed for evolution of the Birmingham Vasculitis Activity Score (BVAS) (A), prednisone dose (B) and forced expiratory volume in 1 s (C) during follow-up. Values are the mean ± SEM. EGPA, eosinophilic granulomatosis with polyangiitis; FEV1, forced expiratory volume in 1 s.

During follow-up, 16 (31%) patients experienced an EGPA relapse on dupilumab, which was associated with blood eosinophilia in 14/16 (88%) cases and led to the discontinuation of dupilumab in 12/16 (75%) patients. Relapses included systemic flares in 10 patients, with constitutional symptoms (n=5), arthralgia (n=4), lung involvement (n=4), myalgia (n=2), nasal crusts (n=2), sinonasal manifestations (n=2), otitis (n=1), glomerulonephritis (n=1), cardiomyopathy (n=1) and gastrointestinal involvement (n=1), asthma exacerbations in five patients and ENT and asthma exacerbation in one patient. Severe manifestations (ie, glomerulonephritis, cardiomyopathy and gastrointestinal involvement) occurred in three different patients. The two patients who relapsed without blood eosinophilia had asthma exacerbations and no systemic flare. Among the four patients who remained on dupilumab despite EGPA relapse, two were started on an additional immunosuppressive agent, one was switched from azathioprine to methotrexate, while the remaining started benralizumab in addition to dupilumab. Of the 16 relapsing patients, 12 (75%) patients had received mepolizumab or benralizumab prior to starting dupilumab, compared with 21/35 (60%) patients in non-relapsing patients. However, the median eosinophil count at the start of dupilumab was significantly lower in relapsing patients than in non-relapsing patients (100 (IQR 0–525) vs 410 (IQR 86–1425) /mm³, $p=0.019$), as was the median time between stopping anti-IL-5/IL-5R and switching to dupilumab (0.5 (IQR 0–1.9) vs 4.7 (IQR 1.3–9) months, ($p=0.017$)).

DISCUSSION

Despite significant advances in the treatment of EGPA with the approval of mepolizumab targeting IL-5 for relapsing or refractory EGPA patients, manifestations related to uncontrolled asthma or, more commonly, persistent nasal polyposis may occur. Importantly, in the MIRRA study (A Study to Investigate Mepolizumab in the Treatment of Eosinophilic Granulomatosis With Polyangiitis),¹⁴ the change from baseline in the Sino-Nasal Outcome Test-22 score at week 52 was approximately –7.5 points, while the minimum clinically important difference is reported to be 8.9 points, and the difference from placebo group did not reach significance, suggesting that anti-IL-5 therapy may be ineffective in some patients.

Dupilumab is a human recombinant IgG₄ antibody that targets the IL-4 receptor alpha subunit (IL-4Ra) and is able to block the signalling pathways activated by IL-4 and IL-13.²¹ IL-4 and IL-13 cytokines play an essential role in the Th2 adaptative responses, known as T2 inflammation, by altering tight junction proteins and thereby increasing the permeability of the epithelial barrier.^{22–23} As dupilumab is approved for the treatment of moderate to severe eosinophilic asthma and CRSwNP, it appears attractive for the treatment of refractory EGPA-related asthma and ENT manifestations. In these studies, transient eosinophilia occurred in the first few weeks and returned to baseline by the end of the treatment period.^{24–25} Early studies in atopic dermatitis showed transient eosinophilia in less than 2% of patients,²⁶ while in a real-world cohort of atopic dermatitis, the mean prevalence of drug-induced eosinophilia with dupilumab reached 9%.²⁷ In severe steroid-dependant asthma, 13% of patients in the dupilumab group had an eosinophil count above 3000/mm³ during the study period, compared with 1% in the placebo group.¹⁷

The efficacy of dupilumab in non relapsing or refractory EGPA-related sinonasal and/or asthma manifestations was 65%, with 41% achieving a complete response and 24% a partial

response. Dupilumab also showed a significant reduction in disease activity as measured by BVAS and prednisone dose. However, a high proportion of patients in our study (66%) experienced eosinophilia on dupilumab. This increase in blood eosinophil count was therefore much more common in our study population than in the phase 3 trials.^{15 17 18} In addition, eosinophilia during dupilumab treatment in our EGPA population was often associated with AEs or EGPA relapses, whereas in the phase 3 trials, clinical AEs were exceptionally observed and occurred only in patients with asthma or CRSwNP.²⁵ However, tapering dose of prednisone does not seem to be associated with the emergence of eosinophilia. Due to the risk of symptomatic eosinophilia, dupilumab was frequently discontinued by physicians in our study. However, tapering dose of prednisone does not seem to be associated with the emergence of eosinophilia. One-third of patients in our study relapsed on dupilumab, half of them with uncontrolled asthma or ENT symptoms and the other half with systemic manifestations. The relapse rate is particularly important given that most of these patients did not have active EGPA when they started dupilumab, raising the question of the benefit/risk balance of dupilumab in EGPA, which remains difficult to answer with these retrospective data. However, it seems very likely that while dupilumab may improve ENT and/or asthma manifestations and have some GC-sparing effect, it has little or no effect on vasculitis manifestations and should probably be avoided in the early months or years of the disease. Identifying the cause of this eosinophilia with dupilumab is complex. As with montelukast and omalizumab, for which a temporal association between these treatments and the development of EGPA has been observed, the question of a direct effect of dupilumab on the relapse of EGPA or, more likely, the effect of tapering the prednisone dose in relation to the improvement of sinonasal and/or asthma manifestations, remains open. Caminati *et al* suggested that the main pathogenetic hypothesis is that while dupilumab inhibits IL-4/IL-13 signalling, it also inhibits eosinophil migration from blood into tissues, resulting in an increase in circulating serum eosinophils,²⁸ supported by the fact that eosinophilia was observed even in patients without a reduction in prednisone dose. Discontinuation of anti-IL-5/IL-5R before starting dupilumab could also be an explanation. Interestingly, although the proportion of patients previously receiving anti-IL-5/IL-5R did not differ between relapsers and non-relapsers, the median eosinophil count at the start of dupilumab was significantly lower in relapsers than in non-relapsers, as was the median time between stopping anti-IL-5/IL-5R and switching to dupilumab. Few cases of new-onset EGPA have been described after switching from an anti-IL-5/anti-IL-5R to dupilumab for eosinophilic asthma.^{29 30} These data suggest that switching from anti-IL-5/IL-5R to dupilumab should be done with caution and that a minimum interval of 3–6 months should be proposed between each biologic.

Finally, we must acknowledge some limitations. This study is a retrospective multicentre study without a control group or standardised GC tapering, which may be associated with a high risk of bias. It provides original retrospective data that are likely to help inform the design and objectives of further prospective studies of dupilumab in EGPA.

In conclusion, this is the largest patient series evaluating the use of dupilumab in the treatment of relapsing or refractory EGPA. In the absence of available prospective data, it provides useful data for clinicians managing EGPA. Our results suggest that in EGPA patients with uncontrolled asthma and/or disabling ENT manifestations and/or GC-dependence, dupilumab may be effective in treating these symptoms and allows GC sparing.

However, the relapse rate is high and relapses are associated with lower eosinophil counts at initiation of dupilumab and a shorter time between discontinuation of anti-IL-5/IL-5R and initiation of dupilumab. Although common transient eosinophilia is often not associated with severe symptoms, eosinophils should be closely monitored to identify patients at high risk of relapse.

Author affiliations

- ¹Department of Internal Medicine, Hospital Cochin, Paris, France
- ²Division of Rheumatology, Department of Medicine DIMED, University of Padua, Padova, Italy
- ³Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
- ⁴Tareev Clinic of Internal Diseases, I M Sechenov First Moscow State Medical University, Moskva, Russian Federation
- ⁵Department of Medicine, Asthma, Allergy and Clinical Immunology, University of Verona, Verona, Italy
- ⁶Department of Respiratory Diseases, Bichat Hospital, APHP Nord-Université Paris-Cité, Paris, France
- ⁷Department of Internal Medicine, Nantes University Hospital, Nantes, France
- ⁸T-reg unit, CNRS, UMR 5525, VetAgro Sup, Grenoble Alpes University Hospital, Grenoble, France
- ⁹Internal Medicine Department, Grenoble University Hospital, Grenoble, France
- ¹⁰Internal Medicine department, University Hospital Ospedali Riuniti, Ancona, Italy
- ¹¹Department of Internal Medicine, Timone Hospital AP-HM, Aix-Marseille University, Marseille, France
- ¹²Department of Internal Medicine, Avignon Hospital, Avignon, France
- ¹³Immunology and Allergology, Institut Central des Hôpitaux, Valais Hospital, Sion, Switzerland
- ¹⁴Department of Internal Medicine, Henri Mondor University Hospital, Creteil, France
- ¹⁵Rheumatology, Institute of Medical Sciences, Uppsala University, Uppsala, Sweden
- ¹⁶Unit of Allergology and Immunology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
- ¹⁷Department of Respiratory Medicine, Regional University Hospital Centre, Tours, France
- ¹⁸Department of Internal Medicine, Besancon University Hospital, Besancon, France
- ¹⁹Coordinating Reference Center for Rare Pulmonary Disease, Department of Respiratory Medicine, Louis Pradel Hospital, Bron, France
- ²⁰Department of Internal Medicine, University Hospital Edouard Herriot, HCL, Lyon, France
- ²¹Nephrology and Dialysis Unit, Meyer Children's Hospital, Florence, Italy
- ²²Department of Internal Medicine, Brest University Hospital, Brest, France
- ²³Internal Medicine, University Hospital Centre, Clermont-Ferrand, France
- ²⁴National Referral Center for Hypereosinophilic Syndrome (CEREO), Department of Internal Medicine, Foch Hospital, Suresnes, France
- ²⁵Department of Internal Medicine and Clinical Immunology, University Hospital Centre, Dijon, France
- ²⁶INSERM, EFS BFC, UMR1098, RIGHT Interactions Greffon-Hôte-Tumeur/Ingénierie Cellulaire et Génique, University of Bourgogne Franche-Comté, Dijon, France
- ²⁷Unit of Immunology, Rheumatology, Allergy, and Rare Diseases (UnIRAR), San Raffaele Scientific Institute, Milan, Italy
- ²⁸Department of Rheumatology and Clinical Immunology, Medical Center, University of Freiburg, Freiburg, Germany
- ²⁹Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Medical University, Graz, Austria
- ³⁰Department Rheumatology & Hiller-Research Unit Rheumatology, Heinrich-Heine-University Düsseldorf, Medical Faculty, Düsseldorf, Germany
- ³¹Department of Medicine, University of Alberta, Edmonton, Alberta, Canada
- ³²School for Mental Health and Neuroscience, Maastricht University, Maastricht, Netherlands
- ³³Department of Medical Sciences and Public Health, University of Cagliari, Monserrato, Italy
- ³⁴Fondazione Poliambulanza Istituto Ospedaliero, Brescia, Italy
- ³⁵Severe Asthma Unit, Careggi University Hospital, Florence, Italy
- ³⁶Department of Internal Medicine, Cochin Hospital, Paris, France
- ³⁷Centre for Inflammatory Diseases, Department of Medicine, Monash Medical Centre, Monash University, Clayton, Victoria, Australia

Twitter Vincent Cottin @#OrphaLung and Maxime Samson @Maxime_Samson21

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ORCID iDs

Berengere Molina <http://orcid.org/0009-0001-4941-9772>

Vincent Cottin <http://orcid.org/0000-0002-5591-0955>

Matthieu Groh <http://orcid.org/0000-0003-0810-136X>

Maxime Samson <http://orcid.org/0000-0002-6547-232X>

Giacomo Emmi <http://orcid.org/0000-0001-9575-8321>

Benjamin Terrier <http://orcid.org/0000-0001-6612-7336>

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