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Eosinophilic granulomatosis with polyangiitis onset in severe asthma patients on monoclonal antibodies targeting type 2 inflammation: Report from the European EGPA study group

To the Editor,

Anti-T2 monoclonal antibodies (mAbs) for severe-eosinophilc asthma have been recently investigated for EGPA.[1] Few cases of severe asthma patients developing EGPA while on omalizumab,[2] benralizumab[3] or dupilumab[4] have been published.

We aimed to describe EGPA onset during anti-T2 mAbs treatment for severe asthma in a multinational cohort. Our retrospective study involving 19 European EGPA Study Group centres from five countries, included patients matching the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria[5] and/or MIRRA trial criteria[6] and diagnosed between June 2017 and June 2022. The study received ethical approval (4085CESC). *T*-test or Mann–Whitney *U* test was applied to compare subgroups. Correlations were explored with Pearson's. Two-sided *p* values of ≤.05 were considered statistically significant. SPSS software was used.

Out of 529 EGPA patients, 30 (5.7%) developed the disease during anti-T2 therapy for severe asthma. Table 1 summarizes demographic, clinical and treatment-related data, as well as the timing of EGPA onset with respect to anti-T2 treatment, which included omalizumab (14 cases—47%), benralizumab (8 cases—27%), mepolizumab 100 mg (4 cases—13%) dupilumab (3 cases—10%) and reslizumab (1 case—3%). Out of the four patients experiencing EGPA while undergoing mepolizumab 100 mg, three had been previously treated with omalizumab. No other cases of EGPA occurred in patients previously addressed to severe asthma therapy switch.

At the time of vasculitis onset, 26/30 patients (87%) were not on oral-corticosteroid, which was suspended several months before (median [IQR]: 10 [4–16]). Furthermore, a significant correlation between blood-eosinophil count (BEC) and BVAS score (R^2 = .270, p = .009) was observed (Figure 1). Figure S1 describes organ involvement at EGPA presentation.

When comparing patients grouped by ongoing biologic treatment at the time of EGPA onset, no significant differences could be highlighted. In particular, the subgroup on anti-IL-5 mAbs (benralizumab/mepolizumab/reslizumab) and the one on dupilumab or omalizumab were similar in terms of patients' age, asthma duration, the timing of EGPA onset in respect of biologic treatment initiation, BVAS and blood eosinophils.

After the induction of EGPA remission, 24/30 (80%) patients were initiated again to anti-T2 mAbs for remission maintenance (Table 1). Of note, 9 patients underwent the same mAb ongoing at EGPA onset (benralizumab-1, mepolizumab-6 and omalizumab-2). Among the 24 subjects restarting treatment with mAbs for EGPA remission maintenance, 1 patient on mepolizumab 300 mg and 1 on mepolizumab 100 mg experienced asthma exacerbation; 1 patient on mepolizumab 300 mg plus omalizumab reported asthma exacerbation and sinusitis relapse; only 1 patient being on anti-IgE therapy suffered from systemic disease relapse (arthralgia, fever, gastro-intestinal symptoms).

Besides the approval of mepolizumab 300 mg for EGPA, real-life data also support benralizumab efficacy and mepolizumab 100 mg relevance, the last in the remission maintenance.[1] Omalizumab and dupilumab molecular targets are less involved in EGPA pathobiology, but still their mechanism of action is unlikely to induce the disease. Of note, dupilumab-induced hypereosinophilia has been speculated as a condition predisposing or accelerating EGPA onset in rare cases of severe eosinophilic asthma patients, after switching from anti-IL-5 mAbs. In that case, a 'rebound effect' on eosinophilic inflammation following a switch from anti-IL-5 to anti-IL-4/13 target therapy and due to the interaction with an alternative immunological pathway might lead to EGPA development.[7] However, in our population, benralizumab or mepolizumab or reslizumab versus dupilumab or omalizumab subgroups were not significantly different in terms of timing of EGPA onset, BVAS and BEC at EGPA diagnosis. The higher number of omalizumab-related cases might rely on its longer availability on the market. The observation is consistent with the results of a large European real-life report on patients treated with biologic drugs for refractory/relapsing EGPA and describing poor performance of omalizumab compared with mepolizumab, with almost half of the patients discontinuing anti-IgE due to therapeutic failure.[8]

Abbreviations: BEC, blood eosinophil count; BVAS, Birmingham Vasculitis Activity Score; EGPA, eosinophilic granulomatosis with polyangiitis; mAbs, monoclonal antibodies.

TABLE 1 Demographic-, clinical- and treatment-related features of the EGPA study population.

Overall study population, N = 30	
Study population by ongoing biologic at EGPA onset	
Omalizumab	14 (47%)
Benralizumab	8 (27%)
Mepolizumab 100 mg	4 (13%)
Dupilumab	3 (10%)
Reslizumab	1 (3%)
Sample characteristics—N (%)	
Males	18 (60.0%)
Age (years)	Min–Max: 40–75 Median [IQR]: 55 [47–67.5]
Former smokers	7 (23.3%)
Current smokers	0 (0%)
Asthma disease duration (years)	Min–Max: 4–62 Median [IQR]: 20 [16–26]
Time from asthma onset to the first biological (years)	Min–max: 0–59 Median [IQR]: 13.5 [6.0–25.2]
Time from biologic starting to EGPA onset (months)	Min–max: 1–60 Median [IQR]: 15 [5–31.7]
Time from OCS stop to EGPA onset (months)	Min–Max: 3–20 Median [IQR]: 10 [4–16]
EGPA features at diagnosis	
BVAS at EGPA diagnosis	Min-max: 4–28 Median [IQR]: 13 [8.5–21]
Eosinophils count (N/μL)	Min-max 980–1800 Median [IQR]: 2390 [1650–5145]
ANCA + (IF)	19 (63.3%)
p-ANCA (IF) WHY not reporting C-ANCA as well? Even if this is 0	100% (of the ANCA-positive patients)
Anti-MPO (ELISA)	14 out of the 19 p-ANCA-positive patients
Anti-PR3 (ELISA)	0
Asthma therapy at EGPA onset	
Inhalation treatment	30 (100%)
Systemic GCs	4 (13.3%)
Montelukast	7 (23.3%)
Treatments for EGPA acute onset	
Corticosteroids	27 (96.4%)
MTX	5 (17.8%)
AZA	6 (21.4%)
MMF	1 (3.6%)
CysA	1 (3.6%)
Cyc	6 (21.4%)
RTX	6 (21.4%)
IvIg	3 (10.7%)
Anti-T2 monoclonal antibodies for EGPA remission maintenance	
Overall	24 (80%)
Mepolizumab 300 mg	8 (33.3%)
Mepolizumab 100 mg	9 (37.6%)
Benralizumab	2 (8.3%)
Omalizumab	2 (8.3%)
Combined mepolizumab 100 mg/omalizumab	3 (12.5%)

Abbreviations: ANCA, anti-neutrophile cytoplasmic antibodies; AZA, azatiophrine; BVAS, Birmingham vasculitis activity score; Cyc, cyclophosphamide; CysA, cyclosporine; EGPA, eosinophilic granulomatosis with polyangiitis; ENT, ear–nose–throat; GCs, glucocorticoids; IF, immunofluorescence; IQR, interquartile range; IvIg, intravenous immunoglobulines; MMF, mycophenolate mofetile; MPO, myeloperoxidase; MTX, methotrexate; RTX, rituximab.

When exploring potential reasons accounting for our findings, the anti-T2 mAbs corticosteroid-sparing effect might provide an explanation. As hypothesized for EGPA onset in asthma patients on leukotriene-receptor antagonists,[9] it may contribute to 'unmask the 'natural' asthma evolution towards a systemic involvement occurring in a proportion of severe asthma patients. In fact, in our cohort, most of the patients had withdrawn corticosteroids at the time of EGPA onset.

Of note, slightly more than half of the patients in our sample demonstrated ANCA positivity at the diagnosis of vasculitis. According to published data, the overall prevalence of circulating ANCA in EGPA characterizes about 40% of patients,[5,10] while in our cohort, it stands at 63%. Given the study design, this finding could naturally be due to chance, making it impossible to draw definitive conclusions. However, recent data from genome-wide association studies (GWAS) have shown differential associations of genetic variants between the two serological subsets. MPO/ANCA-positive EGPA seems to have a significant association with the HLA class II DQ haplotype, which is shared with other MPO-AAVs (e.g. microscopic polyangiitis, MPA), whereas ANCA negativity may be linked to the IL-5/IRF1 loci.[11] For these reasons, it might be interesting to speculate that this higher prevalence of ANCA positivity in our cohort of subjects, who developed vasculitis despite anti-IL-5 therapy, could be the result of a differing ability to prevent the overt development of vasculitis in patients with distinct genetic susceptibility profiles (of which autoantibody positivity might be an expression).

However, the occurrence of EGPA in severe asthma subjects undergoing anti-T2 mAbs we have reported suggests that their ability to interfere with the 'eosinophilic march' by preventing EGPA development remains controversial. On the other side, an increasing amount of literature, mostly related to biologics interfering with the IL-5 axis at the moment, supports the relevance of anti-T2 mAbs in EGPA remission maintenance,[1,10] although long-term data are still lacking. That evidence might have sustained the decision to prescribe again in most of our cases a biologic drug after the EGPA acute phase resolution, which corresponded to the mAb ongoing at EGPA onset for some patients. It further suggests that timing of anti-T2-targeted therapy initiation in respect of the disease stage is crucial, even more when taking into consideration that biologics only partially address EGPA pathobiology.[1] In other words, selectively targeting T2 inflammation cytokines might fail in preventing EGPA

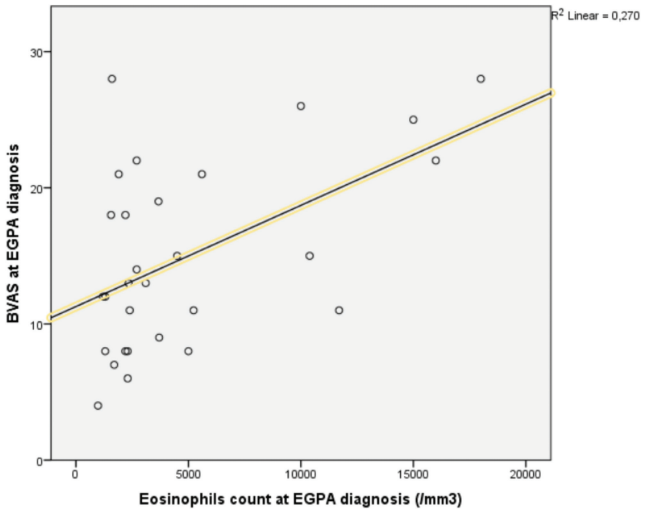

FIGURE 1 Pearson's correlation (BEC and BVAS) at EGPA onset. BEC, blood eosinophils count; BVAS, Birmingham Vasculitis Activity Score; EGPA, eosinophilic granulomatosis with polyangiitis.

occurrence or inducing its remission, but once it has been achieved, it seems to be the most appropriate time for anti-T2 biological drug initiation.

The potential asthma-EGPA trajectory remains unpredictable so far, at least relying on the currently available biomarkers. The study design limits the possibility of exploring in our data potential risk factors of EGPA evolution among the patient's characteristics, which would require to compare our cases with a control group. However, the significant correlation between blood-eosinophil count and BVAS score observed at the time of EGPA onset might suggest to consider BEC increase as a potential marker of disease evolution, especially when occurring in the presence of an anti-T2-targeted therapy. Under that perspective, regularly monitoring eosinophils in severe asthma patients is essential, even more so if an anti-T2 mAbs treatment is ongoing. In fact, if a decrease in BEC is expected, particularly in the case of drugs specifically interfering with the IL-5 axis, and it commonly associates with asthma control, increasing blood eosinophils might represent an early sign of potential disease evolution. Which is not negligible on a clinical ground, in light of the worldwide increasing use of monoclonal antibodies for severe asthma.

Although major limitations, including the lack of a control group and the retrospective design, our report represents the largest focus on the topic so far. Further prospective studies are needed to better characterize EGPA onset in severe asthma patients undergoing anti-T2 mAbs.

AUTHOR CONTRIBUTIONS

MC, MM and GE conceived the paper and provided the first draft. FF performed the statistical analysis. FA, CB, FB, PC, EC, VC, CC, LD, PD, AD, ED, GEF, OK, SM, SaMo, LM, RP, GP, CT, PT and AV collected data and actively contributed to discussion of results and to final manuscript draft.

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CONFLICT OF INTEREST STATEMENT

The Authors declare the following conflicts of interest: C.T. is an investigator in clinical trials with AstraZeneca, GlaxoSmithKline, Sanofi. G.E.-F. received consulting fees from GSK. V.C. received consulting fees from AstraZeneca, GlaxoSmithKline and Sanofi. The other authors declare no conflict of interest in relation to this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

KEYWORDS

benralizumab, dupilumab, EGPA, eosinophilic granulomatosis with polyangiitis, monoclonal antibodies, mepolizumab, omalizumab, reslizumab, severe asthma, T2 inflammation

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.